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SUBDIAPHRAGMATIC VAGOTOMY; INDICATIONS AND TECHNIC

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The principle of vagotomy as described by Dragstedt[1] has been widely accepted in the treatment of peptic ulcer, and the results up to the present time have been satisfactory. During the past year 50 vagotomies have been performed at Cleveland Clinic Hospital, 6 of these through the thorax and the remainder through the abdomen. With increasing experience the subdiaphragmatic approach has become the procedure of choice and has been used exclusively in the last 27 cases.

In a few (7) of the earlier cases only the anterior vagus was sectioned, but more recently both vagi have been severed below the diaphragm, either as the sole surgical treatment of peptic ulcer or more often in conjunction with some gastric operation. At first we did not feel justified in relying too much on vagotomy alone, and in many cases, in order to afford added protection against recurrent ulceration, gastric resection was performed along with vagotomy.

In some cases in which resection would have been difficult or dangerous gastroenterostomy was employed. The excellent immediate results obtained by vagotomy and a conservative gastric operation encouraged us to resect fewer stomachs. Recently I have employed pyloroplasty more often than gastroenterostomy in conjunction with vagotomy (table).

Pyloroplasty is the simplest and safest of all the surgical procedures used in the treatment of ulcer. When employed alone its results were not too encouraging, but when pyloroplasty is combined with vagotomy the immediate results in a small group of cases have been excellent. In many instances pyloroplasty is the easiest means of assuring protection against the development of gastric retention following vagotomy for duodenal ulcer.

Subdiaphragmatic vagotomy has supplanted the transthoracic approach because (1) the abdominal approach allows examination of the ulcer and concomitant abdominal pathosis such as gall stones or hiatus hernia; (2) the abdominal approach enables the surgeon simultaneously to perform some type of operation such as gastroenterostomy or pyloroplasty so that the hypomotility resulting from vagotomy will not result in gastric retention; (3) the abdominal approach is probably safer than the transthoracic; (4) the scar left by the abdominal incision

is less troublesome than the intercostal, where neuralgia sometimes follows resection of a rib; (5) anatomic studies have shown that subdiaphragmatic vagotomy usually can be as complete and effective as transthoracic; (6) the results of subdiaphragmatic vagotomy as indicated by the clinical course of the patients are comparable to those following the transthoracic approach.

The relief of pain following vagotomy has been so prompt and complete that it has been suspected that there may be sensory fibers as well as secretory in the vagus nerve. For this reason I have on two occasions treated patients suffering from "biliary dyskinesia" or so-called "post-cholecystectomy pain" by bilateral vagotomy. Both of these patients had had severe and incapacitating biliary colic for a number of years and have been relieved for twelve and three months respectively since

Table

VAGOTOMY—50 CASES
(Total Clinic Series)

Supplementary Operation	Bilateral Subdiaphragmatic Total 37	Unilateral Subdiaphragmatic Total 7	Transthoracic Total 6
Gastroenterostomy	13	4	1
Gastric Resection	5	3	
Pyloroplasty	3		
Take Down Gastro-enterostomy	3		
Gastric Resection with Pyloric Exclusion	2		
T Tube Common Duct	2		
Cholecystectomy	1		
Repair Hiatus Hernia	1		
Cholecystectomy and Excision Ulcer	1		
No other operation	6		5

operation. A third patient who experienced severe colicky pain in the left upper quadrant has had complete relief following vagotomy but still complains of nausea and vomiting despite the fact that there is no gastric retention. There is a strong psychoneurotic element in this case. Another patient with an inoperable lymphosarcoma of the cardiac end of the stomach experienced severe ulcer-like pain after eating but was completely relieved of pain following bilateral vagotomy. Although the relief obtained in the first 3 cases can be explained on a basis of relaxation of spasm, and although it is possible that hypomotility of the stomach was a factor in the relief afforded to the last patient, it is hard to believe that the pain of a malignant tumor could be alleviated by anything but the severance of sensory pathways.

Vagotomy has had its greatest usefulness in the treatment of marginal ulcers and of ulcers in locations which render their resection dangerous or difficult. It is indeed a boon to gastric surgery to have available a safe and simple procedure which can (1) obviate the necessity of performing total or near total gastrectomies for high benign gastric ulcers, (2) avoid the difficulties involved in taking down gastroenterostomies and performing secondary resections in the treatment of marginal ulcer, and (3) dispense with the danger of injury to the pancreas or common duct or of obtaining an unsatisfactory closure of the duodenal stump during resection of large penetrating duodenal ulcers with foreshortening of the duodenum. In these cases vagotomy alone or coupled with pyloroplasty or gastroenterostomy has saved time, trouble, and probably morbidity and mortality. The diminution of mortality and morbidity has widened the scope of surgery for peptic ulcer and has led us to more frequent recommendation of surgical treatment. The mortality and morbidity of subdiaphragmatic vagotomy alone or in conjunction with a conservative gastric operation is almost certain to be lower than that of gastric resection with removal of two-thirds or more of the stomach.

In dealing with gastric ulcers vagotomy should be used only when the possibility of carcinoma has been excluded by excision or biopsy or when the location of the lesion is such that its removal would entail a greater risk than the possibility of its being malignant. Resection is still the treatment of choice for most gastric ulcers of significant size and possible malignancy.

Postoperative Course

In addition to the safety of the procedure the immediate convalescence of the patient is smoother and more comfortable than that of any comparable group of patients with ulcer treated by gastric resection

alone. Such unpleasant complications as vomiting from gastric retention, distress or feeling of fullness after meals (the so-called "dump syndrome"), and recurrent (marginal) ulceration have not yet occurred following bilateral subdiaphragmatic vagotomy. The pain is relieved from the time of operation, and the appetite is good. The patients are out of bed on the first or second postoperative day. Usually by the eighth day they are eating a liberal diet, are free of symptoms, and are able to go home.

Gastric suction is maintained for the first day or two until it is apparent that the stomach is emptying satisfactorily. In this way overdistention of the stomach is avoided. Even if a gastroenterostomy or pyloroplasty has been done there may be gastric retention, although the symptoms associated with the retention are minimal and soon subside. If no provision has been made to increase the emptying power of the stomach, retention is more apt to be observed, but if the cases in which vagotomy alone is performed are carefully selected this complication should be rare. The only patient in this series who vomited due to gastric retention had a marginal ulcer which had perforated and was closed. Subsequently, without realizing that obstruction was also present, a transthoracic vagotomy was performed. Later it was necessary to relieve the obstruction by reoperating from below. No other secondary operations have been necessary, although there have been a few patients who have had moderate prolongations of the emptying time of the stomach without experiencing any untoward symptoms and without requiring any treatment. Disturbances of the functions of the bowel have not been noted except in 1 patient who has had a persistent diarrhea.

One patient who had a huge duodenal ulcer penetrating deeply into the pancreas and who gave a history of repeated gastric hemorrhages was subjected to vagotomy and gastric resection with removal of the pyloric mucosa and closure of the pylorus proximal to the ulcer. On the fifth postoperative day before there had been time for healing to occur this patient began to bleed again and bled intermittently for two weeks, finally necessitating reoperation and suture of the ulcer. A second but mild episode of bleeding again occurred on the eighth day following the second operation. During this time the patient had experienced no pain, and the bleeding eventually stopped. Although sufficient time had not elapsed since vagotomy to expect healing to take place, this experience raises the question of the efficacy of vagotomy in the treatment of recently bleeding ulcers.

There have been no deaths and no significant postoperative complications other than those listed above.

It is much too early to discuss the end-results of vagotomy. All that

can be said at the present time is that the patients subjected to bilateral vagotomy by Drs. T. E. Jones, R. S. Dinsmore, and myself, with or without complementary operations on the stomach are, so far as we know at the present time, entirely free of symptoms of ulcer and are eating regular diets, are taking no antacid medication, and, if sufficient time has elapsed, have resumed their regular occupations. During the past year the results have been better than those following gastric resection in which vagotomy was not performed.

Surgical Anatomy of the Vagus

Anatomic studies of the vagus indicate that in the majority of cases the vagi form two large trunks above the diaphragm and descend through the esophageal hiatus in the form of two large nerves. Sometimes the main trunks are formed at or even below the level of the diaphragm, and sometimes one or two small branches are given off above the diaphragm and descend through the hiatus with the main trunks. The anterior or left vagus is usually the smaller of the two and is about the size of the lead of a lead pencil. The posterior, or right vagus, is often one and one-half to two times as large.

The anterior vagus lies just below the peritoneum near the midline of the esophagus. The posterior vagus has a more variable position but usually lies behind the middle of the esophagus or slightly to the right. Its relationship to the wall of the esophagus is not so intimate as that of the anterior vagus, and it more often lies in the loose areolar tissue of the posterior abdominal wall rather than in or on the musculature of the esophagus. Sometimes there are several small branches of the vagus given off at about the level of the diaphragm, but usually the nerves do not give off significant branches until they fan out on the wall of the stomach.

Technic of Subdiaphragmatic Vagotomy

The technic is still changing as experience increases and is not as yet standardized. The following deductions are based on my experience in performing 24 subdiaphragmatic vagotomies.

Exposure. Since the esophagus lies high and nearly in the midline it is important to carry the midline incision as high as the position of the xiphoid will allow. A midline incision is not only less vascular and easier to open and close than a left rectus incision, but it also affords a higher and hence a better exposure.

Before proceeding with vagotomy the upper abdomen should be explored, and the operator should assure himself as to the status of the

stomach, duodenum, gall bladder, and esophageal hiatus. It is unwise, however, to perform a gastric operation before vagotomy because soiling from the gastric operation results in contamination of the vulnerable mediastinum and subdiaphragmatic space during the vagotomy. Moreover, if for some reason a satisfactory vagotomy cannot be accomplished, it is possible that the surgeon would elect a radical rather than a conservative gastric operation.

The stomach should be emptied by gastric suction and a Levine tube left in place to aid in identifying the esophagus. It is helpful to pack away the spleen and the fundus of the stomach with a large moist tape inserted into the left upper quadrant of the abdomen.

The left lobe of the liver is sometimes quite large and may interfere with exposure of the vagus. In several of the earlier cases it seemed desirable to divide the avascular diaphragmatic attachments of the left lobe of the liver and reflect it to the right to obtain better exposure of the diaphragm. With increasing experience this maneuver rarely has been necessary. A broad Deaver or malleable retractor inserted under the liver to lift it forward affords adequate exposure.

Identification of the Vagus

The anterior vagus is quite constant in its location and usually can be found with little or no difficulty. The operator stands on the right side of the table. The stomach is grasped in the right hand with a moist tape and retracted downward while an assistant retracts the liver anteriorly with a Deaver retractor to expose the lower part of the esophagus. With the left hand the Levine tube in the esophagus is identified by palpation. Firm downward traction is then exerted on the stomach in such a way that the esophagus is placed on a stretch. The musculature of the esophagus, the peritoneum reflecting from the stomach and the esophagus on to the diaphragm, and the blood vessels of the stomach and esophagus are elastic, whereas the vagus nerve is nonelastic and stands out like a violin string, palpable and often visible beneath the peritoneum. As soon as the nerve is identified by palpation with the index finger of the left hand, the traction on the stomach is delegated to an assistant who maintains it while the peritoneum overlying the nerve is incised and the nerve is picked up on a long nerve hook. Its identity is quite unmistakable, and as soon as it is isolated it can be proved to be the vagus by following it upward through the esophageal hiatus in the diaphragm. The blood vessels of the stomach do not course in this direction nor does the esophageal hiatus transmit any other structure from the thorax to the abdomen. (Fig. 1)

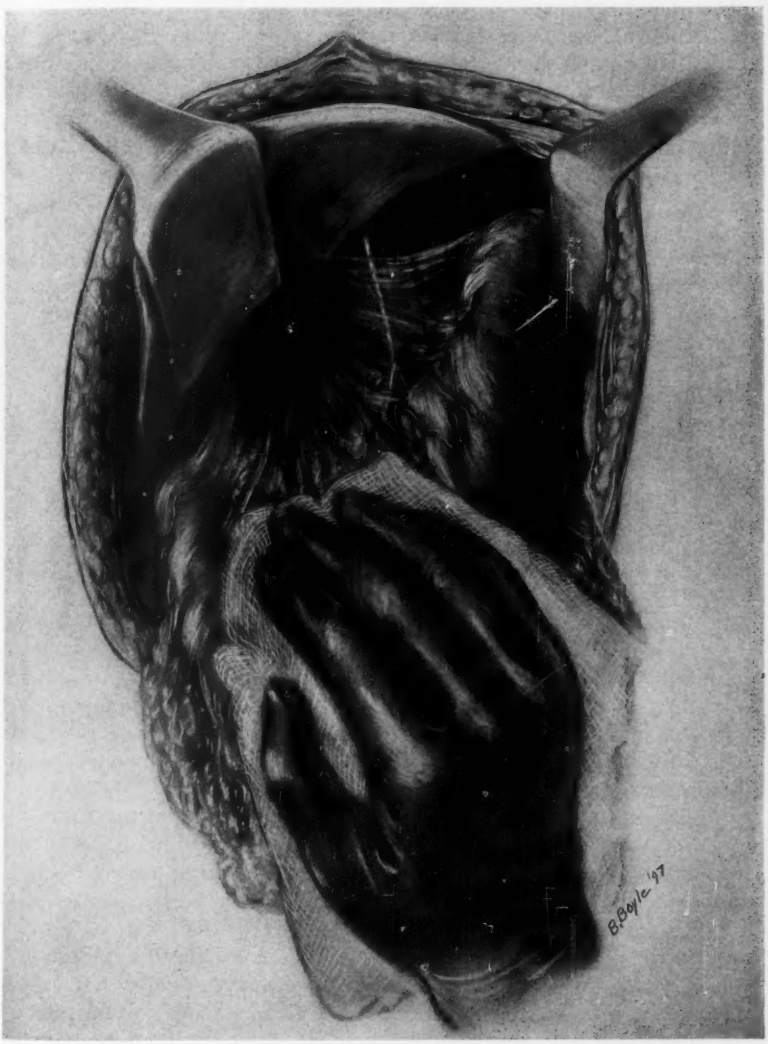

FIG. 1. Anterior vagus seen through peritoneum in its usual position on esophagus.

The nerve is isolated by blunt dissection up to or through the diaphragm and preferably higher so that there will be no question of failure to include all accessible branches. The nerve is then clamped with a Moynihan clamp, divided, and tied with a nonabsorbable ligature to prevent regeneration. The nerve is again divided several centimeters lower and the distal end is disregarded as it does not bleed. The excised segment is examined by the pathologist to prove its identity, but to date the pathologist has not reported anything but nerve tissue.

After completion of the anterior vagotomy the forefinger of the left hand is inserted through the delicate peritoneum of the gastrohepatic omentum above the gastric vessels, as in mobilization of the stomach for total gastrectomy. The stomach is again pulled downward by the right hand, and the posterior vagus is located by palpation as a tense cord lying either on the musculature of the esophagus or more often posterior to the esophagus in the areolar tissue. Occasionally it appears to be more to the right of the esophagus than directly posterior and may be surprisingly far away from it. The nerve is isolated by finger dissection and is then hooked over the finger and withdrawn from its retroesophageal position, this part of the procedure being carried out mainly by the sense of touch. While an assistant pulls the stomach and esophagus downward and to the left, the nerve which is hooked over the index finger of the left hand is picked up by a nerve hook or in a Moynihan clamp and is dissected out, as in the case of the anterior nerve, by blunt dissection. It is important to make certain that it passes upward through the esophageal hiatus since there are vessels posteriorly that could be confused with the vagus if its course through the hiatus is not checked. A segment of the nerve is removed, as in the anterior vagotomy, and the proximal end tied. A final examination of the esophagus should be made to exclude the presence of additional branches coming down from above the diaphragm. (Fig. 2)

Following the vagotomy it is not necessary to reconstruct the peritoneum. Attention is next directed to whatever operation on the stomach is desirable to prevent gastric retention. Pyloroplasty, gastric resection, gastroenterostomy, and local excision of the ulcer each has its place, and the selection must depend on the nature of the ulcer, its location, and on the preferences of the surgeon. Whenever feasible, pyloroplasty would appear to be the operation of choice not only because of its simplicity but also because, if ulceration should recur, gastric resection could be done with ease and without the difficulty involved in taking down a gastroenterostomy. There may be cases in which the duodenum is fixed and foreshortened in which pyloroplasty is not easily accomplished and gastroenterostomy is preferable, but in many cases a simple

FIG. 2. Posterior vagus hooked over finger and brought forward from its position posterior to esophagus.

longitudinal incision through the pylorus and the narrowest portion of the duodenum can be sutured transversely with correction of any tendency to obstruction. Before the pylorus is closed a finger should be inserted first into the duodenum and then into the stomach to make certain that there is no stenosis not correctable by the pyloroplasty.

Complications

In the majority of cases anterior and posterior vagotomy is easily accomplished and does not unduly prolong the operating time. Occasionally in obese patients or when exposure is poor, identification of the nerves is facilitated by slipping a Penrose drain or tape around the esophagus and drawing it downward. I have rarely found this maneuver necessary, and in 1 patient weighing 232 pounds and having a large left lobe of the liver and a high diaphragm, isolation of the esophagus proved to be dangerous. I had inserted my finger through the gastrohepatic omentum and was gently finger-dissecting around the totally unexposable esophagus when I suddenly found that I was lower than I had thought and had inserted my finger through the posterior wall of the stomach where I could palpate the Levine tube. The wall of the stomach in this obese individual, held as it was under tension, had proved much more friable than I would have believed possible. The proposed vagotomy was abandoned, and the small hole in the stomach was closed over as well as possible with fat. Two Levine tubes were left in the stomach with constant suction, and a pyloroplasty was done before closing. The patient was kept in Fowler's position with the tubes in place for four days and made a totally uneventful convalescence.

This case, in which a gastric resection would have been difficult and in which the patient was a poor surgical risk, was the only instance in which technical difficulties have arisen during vagotomy and the only one in which a proposed vagotomy was not completed.

In another case no large posterior vagus trunk could be located, but several small nerves were found and divided. Again on one occasion three, and on a second four separate fairly large trunks were resected, and all proved to be nerves. Only once was a blood vessel cut by mistake, and in this case the bleeding was easily controlled.

Insulin tolerance tests have been done following operation in most of the cases in which gastroenterostomies or gastric resections were not performed, but we have had difficulty in reducing the blood sugars to the desired levels. Although the number of satisfactory tests have been too few to be of statistical value, there has been only 1 case in which the blood sugar fell below 50 mg. per cent that there was a significant rise

in acidity. It is probable, therefore, that in most cases the vagotomies have been reasonably complete. The tendency to retention and dilatation of the stomach which occurs in a high percentage of the cases for the first week or two following operation also indicates that the denervation is adequate to accomplish its purpose.

Summary

1. The immediate results and the subsequent progress of 50 patients subjected to vagotomy have been gratifying.

2. Subdiaphragmatic vagotomy has largely supplanted transthoracic vagotomy because it enables the surgeon to explore the abdomen and if necessary simultaneously to perform an operation to prevent gastric retention.

3. In 32 subdiaphragmatic and 6 transthoracic bilateral vagotomies for ulcer there have been no deaths and only one complication (hemorrhage from a duodenal ulcer on the fifth postoperative day). All followed patients are free of symptoms of ulcer.

4. The excellent early results obtained following vagotomy have led to an increasing use of gastroenterostomy or pyloroplasty with vagotomy. If the results continue to be as good as they now appear, gastric resections will be used less frequently in the treatment of peptic ulcer.

5. A technic of subdiaphragmatic vagotomy is described, and emphasis is placed on the identification of the nerves by sense of touch when they are placed under tension by traction on the stomach.

Since this article was prepared, 27 more patients have been subjected to bilateral vagotomy. Most have had an associated gastroenterostomy or pyloroplasty. Temporary or partial retention has been observed in several of these patients, although in only 1 case have symptoms due to the retention occurred. This patient had no obstruction prior to operation, and nothing was done except a subdiaphragmatic vagotomy. He is still troubled five weeks after operation by a sense of fullness and occasional vomiting.

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HEMORRHAGIC DIABETIC RETINITIS; A METHOD OF TREATMENT BASED ON THE ELEVATION OF PLASMA ALBUMIN BY DIET

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Serious vascular damage used to be considered a complication of diabetes mellitus; it is becoming more generally recognized that this damage is an integral part of the disease. Previously it was hoped that eradication of hyperglycemia with the aid of insulin would prevent what was considered the "complications" of the disease. The careful observation of patients receiving adequate control of glycosuria and hyperglycemia has led to an ever increasing suspicion that this is not sufficient to prevent progressive vascular degeneration. Such progressive vascular disease leads to the tremendous morbidity and high mortality associated with retinal damage, renal failure, coronary artery sclerosis, and gangrene of long standing diabetes mellitus.

With these facts in mind it has become apparent that a clearer understanding of the fundamental processes involved in the accompanying vascular disease is necessary before we can hope for the development of methods for their prevention. No clinical approach to the diabetic patient is complete, therefore, without a careful appraisal of his vascular status from time to time. In our patients a minimum requirement includes careful examination of the retina by an ophthalmologist, an evaluation of renal function, an estimate of any change in the peripheral vessels, determination of cardiac status, and frequently the taking of an electrocardiogram.

Up to the present time our chief interest in this regard has centered upon the vascular disease of the retina. Particular attention has been given to the study of alteration in plasma proteins which might be a contributing factor in the production of retinal hemorrhage.

Abnormally low levels of plasma albumin might be expected to accentuate a tendency to perivascular exudation and hemorrhage. Induced

hypoproteinemia in rabbits prior to the induction of alloxan diabetes has been observed[1] to result in a striking tendency toward retinal hemorrhage.

It had been previously pointed out [1,2,3] that in patients with diabetic retinitis plasma proteins are characterized by low albumin and high beta globulin in the presence of total protein values which are normal or only slightly reduced. Similar changes are present in some patients with uncontrolled diabetes mellitus without retinitis. The plasma albumin levels in these two groups respond quite differently to treatment. In the second group with little or no evidence of vascular disease of the retina, "adequate treatment"[3] on diets containing 60 to 70 Gm. protein per day promptly restores the plasma albumin level to normal. In the former group with apparently more vascular disease, plasma albumin levels were not readily corrected. Much higher protein intake, ranging from 100 to 200 Gm. per day, must be added to the routine for many months before normal albumin levels are obtainable.

A representative group of 30 cases of diabetic retinitis has been analyzed for the present paper. In each instance the characteristic plasma protein pattern previously described was present. These patients have been selected not because of age, sex, duration or severity of their existing diabetes but because they have had abnormalitities in plasma protein pattern. This condition has been present in the majority of a larger group of patients with diabetic retinitis previously studied by us.

By the methods used, normal values for total plasma proteins and their fractions can be defined within a range which can be determined accurately. Our own experience with 21 normal subjects[4] has shown the following range:

	Total Protein	Albumin	Beta Globulin
Range	7.82 5.94	5.11 3.72	1.07 0.65
Average	6.51	4.09	0.81

These values correspond closely with those reported by Longsworth *et al.*[5] and Luetscher.[6]

The plasma protein values in the group of patients with diabetic retinitis under consideration were as follows:

	Total Protein	Albumin	Beta Globulin
Range	7.95 5.34	4.19 2.28	1.58 0.94
Average	6.38	3.01	1.15

Accompanying abnormalities observed in the alpha and gamma globulin fractions and fibrinogen are left for future consideration.

An attempt has been made to raise the low plasma albumin levels to normal by increasing the protein intake while maintaining good control of hyperglycemia. When diabetic retinitis is present it frequently proves very difficult and, in our experience, sometimes impossible to completely correct this abnormality. Diets containing 100 to 200 Gm. of protein per day must be used for many months before strictly normal albumin levels are obtained.

A diet of this type containing 140 Gm. protein per day follows: skimmed or whole milk 1000 cc., 1 egg, lean meat 210 Gm., and casec 50 Gm. The remaining protein is present in bread, crackers, and vegetables.

The protein intake can be increased to 200 Gm. per day by a diet prescription as follows: 7 eggs, bacon 20 Gm., milk 1000 cc., lean meat 300 Gm., and casec 40 Gm., with added bread and vegetables.

In 16 of the 30 patients in this group we have had an opportunity to observe the degree of success attained in correcting the low plasma albumin level by such diets. The values before as compared to those found several months after this additional treatment are as follows:

		Total Protein	Albumin	Beta Globulin
Before	Range	7.95 5.34	4.19 2.28	1.58 0.94
	Average	6.38	3.01	1.15
After	Range	8.22 6.04	4.95 3.28	1.55 0.82
	Average	7.1	3.84	1.19

Complete correction of the lowered albumin level was obtained in 10 of the 16 patients. Uniformly successful results occurred only when diets supplied over 100 Gm. protein per day and were taken for six to eighteen months. In 1 instance a fall in albumin occurred while 130 Gm. protein was consumed over a nine-month period. The level subsequently rose on 200 Gm. protein consumed daily for seven months. In general, a rise to normal plasma albumin level accompanied daily intakes of 100 to 120 Gm. Slower rises occurred in a few patients on 80 Gm. per day. In others the same amount of protein was insufficient to maintain the albumin fraction at a stationary level.

The albumin level in the remaining patients failed to show complete recovery during the period of observation on increased protein intakes. One of these had severe hypertension and renal insufficiency; 1 had poor control of hyperglycemia during the last four months of study; 1 received only 80 Gm. protein per day, and 2 were followed for five months or less. These factors, we believe, completely or partially explain failures in the correction of albumin levels.

The elevated beta globulin fraction was not significantly altered by the increased protein prescribed. The significance of this abnormality in plasma proteins is not yet understood.

The retinal findings are of considerable interest in the 10 patients in whom a normal albumin fraction was obtained by this method of management. During the period of observation 7 of these 10 patients showed improvement in that there were fewer or no hemorrhages; the other 3 showed no improvement. These 3 all had proliferating retinitis. The degree of improvement demonstrated by the 7 cases can be judged by the following notes.

One patient originally demonstrated frequent hemorrhage, exudate, edema, optic atrophy, and marked contraction of both form and color fields. After three and a half years of treatment she had only an occasional petechial hemorrhage, no exudate or edema, slight haziness of the optic disks, normal form and color fields, and was able to thread a needle.

A second patient had no hemorrhages eight months after the albumin level had become normal. Visual acuity improved, and the retinae showed only highly refractile bodies. A third patient originally showing numerous hemorrhages had none at the end of two years when the albumin level was normal. The fourth and fifth patients were observed for sixteen months, during which time fewer hemorrhages occurred, and 1 of these had none during the last six months of observation. The sixth and seventh patients were observed for three years before albumin levels became normal. One of these had no hemorrhages at the end of this time. The other still presented occasional petechial hemorrhages.

It appears obvious that factors other than plasma albumin levels are very important, since retinal hemorrhage continues to occur in some patients in spite of normal albumin levels. Further, in view of the high casein diets we have used it is interesting to reflect that rats on choline deficient diets develop not only renal but retinal hemorrhage [7,8] and that such food factors as may be supplied in diets containing large quantities of casein, methionine, and labile methyl groups are intimately associated with such changes.

Conclusions

1. Abnormally low levels of plasma albumin have been found to be an almost constant accompaniment of diabetic hemorrhagic retinitis in patients studied at this Clinic.

2. Low plasma albumin levels by causing a lowered osmotic tension increase the tendency to exudation and hemorrhage.

3. A method has been described by which such low levels of plasma albumin may be raised by the use of high protein diets.

4. Such factors as poor diabetic control, too short a period of treatment, or renal failure may interfere with the efficiency of such management.

5. In 16 patients treated for two to three and one-half years, the plasma protein pattern was corrected in 10, recurrent retinal hemorrhages were eliminated in 6, lessened in 1.

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NEOPLASMS OF THE SMALL INTESTINE

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Neoplasms of the small intestine constitute only a small percentage of the tumors found throughout the gastrointestinal tract, but they are discovered frequently enough to make the clinician "small bowel conscious". Certainly this type of lesion should always be considered when a patient is seen with obscure intestinal symptoms or with bleeding from the bowel of undetermined origin. Ewing[1] states that carcinoma of the small intestine is comparatively rare, forming about 3 per cent of all intestinal cancers. Tumors of this type constitute the majority of the small intestine neoplasms. The next most common type is that of the sarcoma group. Sarcoma may occur in any portion of the small intestine but is seen more often in the ileum. A third type of neoplasm to be considered is the carcinoid or argentaffin tumor which is also seen with greater frequency in the ileum than in the proximal portion of the small intestine. These tumors are usually small intramural growths and seldom give rise to clinical symptoms. They are seldom discovered by roentgen examination and are more apt to be seen at autopsy or as an incidental finding at operation.

Many tumors of the small intestine are not definitely diagnosed before operation because a special roentgen examination of the intestine has not been made. Instead, and with some logic, the diagnosis is made by an exclusion process following a negative roentgen examination of the stomach and colon. Considering the rarity of tumors of the small intestine, it is readily understood why they may not be considered when the patient is first seen, and how they may be overlooked in the routine roentgen examination of the gastrointestinal tract. This is particularly true with small tumors or those outside of the bowel lumen, and diligent search must be made by careful roentgen examination which is not only time consuming but may also be somewhat tedious.

The symptoms will vary greatly, depending upon such factors as type of tumor, size of the mass, degree of encroachment on the lumen and its location. During the early stage of growth and even after the tumor has reached considerable size, the subjective symptoms may be so slight or obscure that they are apt to be disregarded by both the patient and the clinician.

The most common symptoms of malignant tumors of the small intestine are those due to mechanical obstruction and to intestinal bleeding. The former is more often seen in the carcinoma group since

these tumors arise in the mucosa and are primarily of the intraluminal type. Obstruction may be produced by constriction of the lumen from the classical "napkin ring" type of growth or by encroachment upon the lumen of the bowel by a projecting mass. The early symptoms are those of obstruction and may consist only of vague, colicky pains or a subjective feeling of peristaltic unrest. Frequently nausea may be the chief symptom. As growth progresses, however, obstruction increases with constipation, nausea and vomiting, signs of abdominal distention, and visible peristaltic movements. Where, however, the carcinoma has arisen from a pedunculated adenoma, the onset may be sudden and severe due to an intussusception and the resulting obstruction.

The small intestinal tumors occurring outside the lumen are mostly of the sarcoma type. They may not give rise to early symptoms since there may be little or no encroachment upon the lumen of the bowel until they have reached considerable size. With the enlargement, they may either project into the lumen and produce obstruction, or the obstruction may result from pressure of the large mass outside the lumen. With this type of tumor a palpable mass may be present in the abdomen with only mild subjective symptoms suggesting an obstructing lesion.

Intestinal bleeding is frequently found to be due to a malignant tumor although it may not appear until the growth is of considerable size. The bleeding may be manifested as occult blood or hypochromic anemia, but massive hemorrhage with tarry stool or even bright red blood is not uncommon. Again, the type and location of the growth are important factors in causing bleeding. The carcinoma group, because of early mucosal involvement, will give rise to bleeding early. The group arising outside the lumen, on the other hand, may be present for a considerable time before the mucosa is invaded and ulceration produced.

The age of patients with neoplasm of the small intestine is a suggestive but not an entirely dependable factor in diagnosis, although the carcinoma group more commonly occurs in the fourth and fifth decades of life. In the sarcoma group the incidence is higher in the fourth decade although it may occur from infancy to an advanced age.

The roentgen examination is the most important procedure for diagnosis of lesions of the small intestinal tract and any one, or a combination, of three technics may be employed. These consist of barium by mouth with interval examination, the so-called "small intestinal enema" with duodenal intubation, and the barium enema into the colon. Examination in the last procedure depends upon sufficient barium mixture passing through the ileocecal valve for visualization of the distal portion of the ileum. Of these procedures, the first named is of more value for lesions in the proximal and mid-portions, and the last for

visualization of lesions in the distal or terminal portion of the ileum. We have employed the intubation technic but a few times since we have found it difficult to obtain satisfactory visualization. Due to the extent of the bowel which is filled with the barium solution at one time, there is considerable overlapping of the various loops of intestine with resulting confusion of shadows.

The usual procedure at Cleveland Clinic when a lesion of the small intestine is suspected is to examine the patient by the oral route first and follow this with the barium enema. Although the examination may follow the same pattern, no routine can be established since this will depend upon time of passage of the barium solution through the small intestine and the conditions which may be demonstrated. In all cases, however, we use only a small amount of the barium solution, as a rule not over 2 ounces of a thin suspension. This is an important point since it is desirable to obtain adequate visualization and avoid overlapping of the intestinal loops which will occur if a large amount of the barium mixture is given to the patient. The patient drinks the solution in small sips during the initial fluoroscopic examination so that the proper amount may be determined. At this time careful examination of the duodenum and proximal jejunum is made and spot films exposed if any abnormal changes are noted. Following the initial fluoroscopic examination, survey films are made with the patient in the most appropriate position for demonstration of any changes noted. The study is then continued at intervals, which will vary from minutes to hours, depending upon the rapidity with which the barium solution passes through the intestine and upon the discovery of any lesion that may be demonstrated. For this reason every examination of the small intestine is an individual problem and no routine method or procedure may be established.

Both fluoroscopy and films are employed; the former is of importance for manipulation and separation of the various loops, the latter for record and detailed visualization. The column of barium is followed at least until the head of the meal has reached the cecum and all parts of the small intestine have been adequately visualized. In some patients a marked hypermotility may be present and the barium will reach the colon in an hour or less. In others there may be obstruction or hypomotility and a period of hours may be required for complete examination. In a great many cases, some of which may be normal, there may be some delay or slowing in the motility when the meal has reached mid-portion of the bowel. If there is no residual barium in the stomach at this time the patient may eat a light meal which will again stimulate intestinal activity and speed the passage of the barium column. In

every case we include a six-hour film, regardless of others that have been made, since this forms the basis of our judgment of the over-all motility. It can be readily understood that the complete examination requires considerable time and attention but there are no short-cuts if one is to arrive at the correct diagnosis.

The barium enema examination is employed if a lesion has not been demonstrated by the preceding method. Generally it will permit more satisfactory visualization of the distal and terminal portion of the ileum by reflux of the barium through the ileocecal valve. In the interval study method it may be difficult to obtain satisfactory visualization of the terminal ileum due to overlapping and inability to separate the partially filled coils. This difficulty is overcome to a considerable degree by the distention of the lumen with the barium solution at the time of the fluoroscopic examination. The distention tends to straighten the intestinal coils. This effect, combined with manipulation of the gloved hand, will give satisfactory visualization of a considerable length of the distal ileum.

At times the barium suspension in the colon may obscure the ileum and in these instances the patient should have additional fluoroscopic

Fig. 1. Adenocarcinoma of ileum. Annular constricting deformity producing partial obstruction. Dilatation of intestine proximal to the lesion.

examination and roentgenograms after expulsion of the enema. Generally, too, the patient is more relaxed after expelling the solution and it is possible to make a more thorough search for the suspected lesion.

The roentgen criteria for diagnosis of neoplasms of the small intestine are much the same as for the other portions of the gastrointestinal tract. The most prominent change will be a localized deformity of the shadow which may manifest itself as a filling defect, an annular constriction, or an infiltrative defect in the wall of the bowel. Although lesions other than neoplasm may simulate some of these changes, filling defects due to tumor are generally sharply demarcated at both the proximal and distal margins and involve a short segment. Other changes associated with neoplasm are alteration or obliteration of the mucosal pattern at the site of the lesion, obstruction, and ulceration.

Obstruction may develop slowly over a period of time and will show an increasing degree of dilatation of the bowel proximal to the site of the lesion. In the early stage of obstruction such as that produced by a constricting neoplasm (fig. 1), the dilatation may not be marked and may be demonstrated for only a relatively short distance proximal to

FIG. 2. Adenocarcinoma of jejunum causing obstruction. There is marked dilatation of the duodenum with loss of morphologic characteristics of the tumor.

the tumor. As the obstruction and resulting dilatation increase, however, it may reach such a degree that the morphologic features of the lesion cannot be demonstrated by the roentgen examination (fig. 2). The characteristic appearance of intestinal obstruction with marked dilatation, "stepladder" pattern, and multiple fluid levels is usually absent unless there be sudden onset such as that produced by intussusception of a polypoid tumor. This is due chiefly to the fact that the small intestine has the inherent ability to compensate for a gradual reduction in the diameter of the lumen.

Mucosal pattern change may be one of the earliest manifestations produced by neoplasms of the gastrointestinal tract. In the carcinoma group, arising from the mucosa, this will be the first demonstrable change in the roentgen examination. With the intramural type of tumor and the one arising outside the lumen, the mucosal pattern change is produced by pressure or stretching of the folds and may not be marked at any stage. These changes are best demonstrated during the fluoroscopic examination and must be carefully looked for throughout the length of the small intestine. As the growth of the tumor progresses and

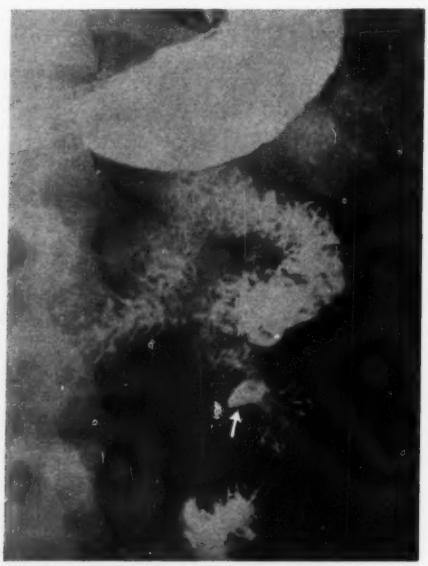

FIG. 3. Leiomyosarcoma of the jejunum. Tumor intramural in origin but growth did not project into the lumen. Ulcer crater and slight ulceration of mucosal pattern are only roentgenologic sign of this tumor; measurement 6 x 4 x 3 cm.

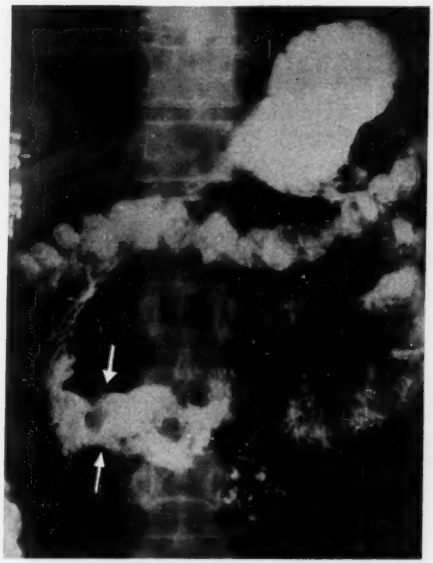

FIG. 4. Lymphosarcoma of duodenum. Infiltration of wall of intestine producing marked irregularity with a little dilatation. Absence of mucosal pattern due to invasion by neoplasm. Segment involved longer than with carcinoma.

its size increases the pattern may be completely obliterated even though the mucosa has not been invaded by the lesion. With invasion of the mucosa, ulceration will be present (fig. 3), and this may be the only evidence of a neoplasm which has developed external to the lumen of the bowel. In the case which was recently reported by Collins,[2] the mass of the tumor was external to the lumen and no evidence of obstruction was present. Apart from the ulceration there was only slight alteration in the pattern of the mucosa and the lesion could easily have been overlooked had it not been for visualization of the crater.

The filling defects of neoplasm show morphologic characteristics which place them in one of three groups; the infiltrative defect, the annular or constricting defect, and the polypoid mass. The infiltrative defect is more common in lesions which are intramural in origin, of which lymphosarcoma (fig. 4) is an example. These tumors may show involvement of a rather long segment of intestine when they are first discovered and may even resemble inflammatory changes in the roentgenogram. Ulceration may or may not be present, as in many cases the mucosa may not be destroyed even though the infiltration be extensive.

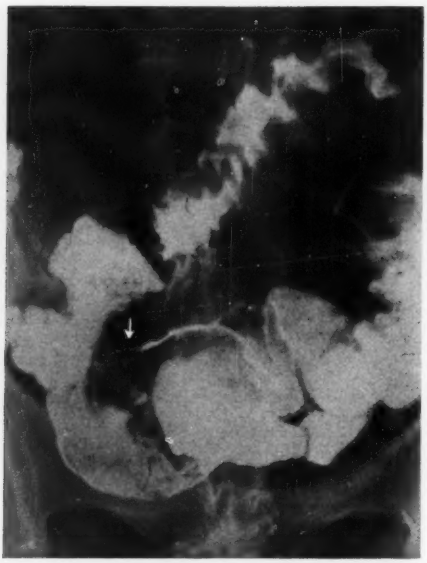

Fig. 5. Spindle cell sarcoma of ileum. On examination of colon neoplasm visualized by reflux barium through ileocecal valve. Tumor almost entirely outside of the bowel but produced polypoid filling defect by pressure on the lumen.

Rigidity of the intestinal wall is apparent during the roentgen examination and this feature is especially prominent during the fluoroscopic examination. It is during this phase of the examination that the lack of peristaltic movement through the involved segment is most striking. The lumen may show narrowing as well as infiltration but this is not always true in neoplastic disease. The annular defect is highly suggestive of carcinoma, particularly so if the appearance is that of a "napkin ring" deformity with involvement of a short segment. These appearances must be differentiated from inflammatory changes. In the latter condition the involved segment is usually longer and the margins of the process are not so sharply defined. Also with inflammatory lesions there may be surrounding adhesions which are demonstrable at the time of fluoroscopic examination by fixation of the bowel. With involvement of a short segment in inflammatory disease or a longer segment in the case of neoplasm, it may be impossible to make a definite diagnosis before operation.

Polypoid filling defects are, as a rule, well-defined negative shadows within the lumen of the bowel and are most often due to tumor of

mucosal origin. Tumors of intramural origin may simulate this appearance if they project into the lumen of the bowel in the course of their development (fig. 5). Benign tumors most frequently present a polypoid appearance and with no other changes present it may be possible to differentiate them from malignant tumors.

Conclusion

Malignant tumors of the small intestine, although not common, should be considered in patients having obscure gastrointestinal symptoms or intestinal bleeding from undetermined origin. These tumors show the same morphologic characteristics as they do elsewhere in the gastrointestinal tract, and a high percentage may be diagnosed by special roentgen examination.

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THE USE OF CURARE AND PENTOTHAL SODIUM IN ENDOSCOPY

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The difficulties encountered in endoscopic examination of certain individuals are well known to all who are actively engaged in this type of work. In a short heavy-set person with a thick neck, it is often very difficult to obtain a satisfactory view of the larynx. In people who are excessive smokers and have a hyperactive gag reflex, it is very difficult to obtain sufficient anesthesia with topical applications alone for a satisfactory examination. This is also true of the hypersensitive, apprehensive person who lives in a state of nervous tension. When these patients submit to an endoscopic examination they are subjected to a maximum of psychic trauma, and in many instances the examination or operative procedure cannot be carried out satisfactorily.

The various general anesthetics now in common use have been employed at one time or another for endoscopic procedures. Certain disadvantages have accompanied the different agents employed:

1. Instrumental manipulation of pharynx and larynx has frequently resulted in a laryngospasm.

2. Deep anesthesia is required to produce sufficient relaxation to accomplish the examination.

3. The deep anesthesia thus produced causes a prolonged recovery period. This precludes the possibility of the examination's being accomplished on an out-patient basis.

Pentothal sodium anesthesia alone has been found to be very satisfactory for endoscopic procedures in the difficult patient. However, there are certain dangers and disadvantages to its use owing in part to the fact that it does not afford complete anesthesia. Any irritation in the pharynx and larynx of a patient anesthetized with pentothal sodium is likely to produce a laryngospasm which may prove troublesome but never dangerous to a competent endoscopist. However, this can nearly always be avoided by instilling a local anesthetic into the larynx and trachea just before induction of anesthesia. In addition, to produce sufficient relaxation fairly deep anesthesia is required. Deep anesthesia

is undesirable and may be dangerous. Furthermore, this type of anesthesia is not well tolerated by children. However, the smooth, pleasant, rapid induction and rapid recovery make pentothal sodium an extremely desirable agent.

One of the important advances in anesthesiology has been the supplementing of a general anesthetic agent with curare. There has been a large volume of material in the recent literature on curare* and its use in various surgical procedures as an adjunct to other forms of general anesthesia. Its property of producing relaxation of the skeletal muscles by bringing about a temporary paralysis led us to try it in combination with pentothal sodium for endoscopic procedures.

The pharmacologic action of crude curare has been described by many authors, but the actual mechanism by which it blocks the transmission of the nerve impulse at the myoneural junction is not fully known. Most investigators believe that curare interferes with the normal action or production of acetylcholine. Curare exhibits its effect on striated muscle but has little or no effect on smooth or cardiac muscle. Crude curare has been known and used experimentally for many years, but not until recently has it been produced in a sufficiently pure and standardized form for clinical use.

Curare is known to affect the muscles of the body in the following order:

1. Muscles innervated by the cranial nerves.
2. Muscles of the extremities and trunk.
3. Muscles of respiration, the last being the diaphragm.

Since one of the first actions of curare is to relax the muscles of the pharynx and neck, it is especially applicable to endoscopic procedures. Thus, only the minimum dose of the drug is required to obtain this desired effect. This margin of safety is further increased by the rapidity of excretion. If an overdose should be administered, artificial respiration can be instituted until spontaneous respiration returns. Furthermore, the toxic effect of the drug is rapidly counteracted by an intravenous injection of neostigmine.

Method of Administration

Precautions are taken to ensure an empty stomach. This lessens the possibility of vomiting during the administration of the local anesthetic and the danger of aspiration of stomach contents during general anesthesia or the recovery period.

*The curare preparations used by the method described in this paper are intocostrin (Squibb) and d-tubocurarine chloride (Abbott).

For premedication 1½ gr. of pentobarbital sodium is given from one-half to two hours before the procedure. Morphine sulfate 1/6 to 1/4 gr. and atropine sulfate 1/150 to 1/75 gr. is administered by hypodermic injection one-half to one hour before administration of the anesthetic.

Local anesthesia is accomplished by spraying the mouth and pharynx two or three times with 2 per cent pontocaine solution. Topical applications of 10 per cent cocaine solution are made in both pyriform recesses. Three or 4 cc. of 2 per cent cocaine solution is then instilled into the trachea, care being taken not to use more than 0.5 to 1 cc. at a time. This precaution in the instillation will prevent rapid absorption into the blood stream, and so-called "cocaine reactions" will seldom occur. If after each instillation the patient is encouraged to cough, the cocaine will be distributed over the tracheobronchial mucous membrane, providing better anesthesia and allowing only a small amount of alveolar absorption. The patient is then placed on the operating table and prepared for the endoscopic procedure in the usual manner.

One forearm is fixed in supination to an armboard by means of adhesive tape. The curare is given as the first step in the induction of the anesthesia, as its action does not appear until three or four minutes after injection, whereas the effect of the pentothal sodium is noted within thirty seconds. The needle to be used for the venipuncture is affixed to a 5 cc. syringe containing 3 cc. (60 units) of the curare preparation. The needle is inserted into the vein and the curare injected. The needle is flushed once or twice by the aspiration and reinjection of 2 cc. of blood, and the syringe is replaced with another containing 20 or 30 cc. of pentothal sodium in 2.5 per cent solution in distilled water. The flushing of the needle avoids the formation of the precipitate which results from mixing the two drugs in the concentrations used. Pentothal sodium anesthesia is induced in the usual manner, and after the lapse of four or five minutes the endoscopic examination may be begun. If the relaxation proves insufficient, an additional 2 or 3 cc. of curare may be injected after flushing the needle and rubber tubing, if employed, by a few cubic centimeters of physiologic saline solution. If the respiration is depressed by partial paralysis of the diaphragm, artificial respiration may be carried on by gentle intermittent manual pressure over the lower chest (sixteen times a minute, or synchronous with the diaphragmatic contractions). If the condition persists after the conclusion of the endoscopy, neostigmine 0.5 mg. should be given intravenously. Neostigmine acts as a physiologic antidote to curare by inhibiting cholinesterase from destroying acetylcholine. Administration of pentothal before the maximum effect of the curare has taken place avoids the unpleasant

choking sensation experienced when the muscles of the pharynx and neck are paralyzed in the conscious patient.

This method of anesthesia was used in 50 cases including 23 direct laryngoscopic, 11 bronchoscopic, and 5 esophagoscopic examinations. In our cases from 2 to 6 cc. of curare was used. Relaxation was not sufficient in the case in which only 2 cc. of curare was used and only fair in 2 of the cases in which 3 cc. was used. In all others, the relaxation and exposure were excellent. In none of the cases was there any laryngospasm or cessation of respiration. No vomiting occurred either during or after the procedure. After examination the patients were placed in a recovery room and were not allowed to leave the hospital for two or three hours and then were accompanied by a relative or friend.

This type of anesthesia is not recommended for all endoscopic procedures. In our last 100 endoscopies the curare-pentothal combination was used only thirteen times. It should be reserved for those in which difficulty in obtaining relaxation or cooperation is either anticipated or encountered. It should be given only by a competent anesthesiologist, and equipment to combat apnea and hypoxia must be readily available.

GASTROCOLIC FISTULA: A NEW CONCEPT OF PATHOLOGIC PHYSIOLOGY; MECHANISM OF PRODUCTION OF THE SYNDROME*

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The pathologic physiology in gastrocolic fistula has not been fully explored, and there are conflicting opinions as to the mechanism which produces the syndrome.[1,2,3,4,5] Gastrocolic fistula does not occur frequently, but it is one of the most dreaded complications of surgical treatment for peptic ulcer. It may produce a devastating syndrome which includes diarrhea, weight loss, malnutrition, anemia, and steatorrhea.

Haller[6] described the first case of gastrocolic fistula in 1755, and in 1903 Czerny[7] made the first report of fistula following gastrojejunal ulcer. Voorhoeve[8] collected 103 cases in the literature in 1912.

As the utilization of gastroenterostomy in the treatment of peptic ulcer increased the incidence of gastrojejunocolic fistula secondary to jejunal ulcer increased. Atwater, Butt, and Priestley[9] reported that 11 to 14 per cent of gastrojejunocolic ulcers finally develop into gastrojejunocolic fistulae. In their series of 42 cases, 40 were secondary to gastrojejunal ulcer following surgical treatment of peptic ulcer, and 2 were the result of carcinoma. There are other causes for gastrojejunocolic fistula, but they are rare. These include tuberculosis, syphilis, ulcerative colitis, peritoneal abscess, trauma, and congenital deformities.

Direction of the flow of aliment has been the subject of much discussion. Earlier workers [8,10] accepted fecal vomiting as evidence of a flow of colonic contents into the stomach. Other authors indicate that the flow is largely from the stomach to the colon. They believe that the shunting of food through the fistula from the stomach into the colon is a major factor in the production of the syndrome.[4,9,11,12]

In 1920, Bolton and Trotter[1] made an important observation. They observed rapid improvement in the patient's condition after making a temporary cecostomy for treatment of gastrojejunocolic fistula. They stated, "It was also clear that the direction of flow was from the colon into the stomach and not vice versa, as no undigested food or excess of

*This is part of a thesis submitted by Dr. Kiskaddon in fulfillment of fellowship requirements and awarded the William E. Lower Prize.

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fat was present in the faeces", and "The passage of the colonic content along the small intestine no doubt was responsible for the diarrhea."

Pfeiffer and Kent[2] reported similar observations on flow of aliment and the clinical improvement of the patient following colostomy proximal to the fistula. They believed that the diarrhea was caused by fecal irritation of the stomach and intestines. Mathewson[5] also disagreed with the common concept that diarrhea was due to emptying of acid contents into the colon. Other authors reported clinical improvement in patients having other types of operations to prevent or interrupt the flow of fecal material to the fistulous region. Lahey and Swinton[13] and Lahey and Marshall[14] accomplished this result by "internal colostomy". Baker[3] produced the same effect with ileostomy. The result of these procedures was not only improvement in the patient's condition but cessation of the diarrhea, although the fistulous communication between the colon and the stomach was still present. This evidence would suggest that a condition other than shunting of food from the stomach into the colon might be responsible for diarrhea and production of the syndrome.

The problem of steatorrhea in patients with gastrojejunocolic fistula was investigated by Strauss in 1921.[15] After making extensive chemical analyses of the stools of 2 patients he concluded that there was poor absorption of fat in the presence of adequate secretion of pancreatic ferments.

Anemia has also been an interesting problem in cases of gastrojejunocolic fistulae. Although most of these patients have microcytic hypochromic anemia, a small percentage of them develop a macrocytic type. It is interesting in this connection to recall the hypothesis of Knud Faber[16] concerning the mechanism and production of pernicious anemia in patients having strictures of the small intestine. He believed that gastric achylia permits bacterial growth in the stomach and duodenum, and as a result bacterial decay permits absorption of intestinal poisons which gave rise to pernicious anemia. Meulengracht[17,18] reported 10 such cases and attributed the anemia to absorption of hemotoxic material through the damaged mucosa. Seyderhelm, Lehman, and Wichels[19] made strictures in 10 dogs, 4 of which developed hyperchromic anemia. The authors also reported upper intestinal contamination with Escherichia coli. All this evidence suggested to us that in gastrojejunocolic fistula regurgitation of fecal contents through the fistula into the stomach might in some way damage the absorptive and digestive functions of the small intestine, thereby producing a sprue-like syndrome.

In the literature there are few references to morbid changes in the intestine in cases of gastrojejunocolic fistula.

In 1940, Colp[20] mentioned hypertrophy and injection of the stomach and jejunal mucosa, but there was no reference to histologic changes remote from the gastrocolic fistula.

Because of conflicting opinion and because shunting of food from the stomach into the colon did not seem to provide an adequate explanation for the syndrome, we reviewed the clinical records of 20 patients with gastroenterocolic fistula seen at Cleveland Clinic between February, 1921, and February, 1946. We made gastroenterocolic anastomoses in dogs to observe the findings and to compare them with those in human patients having similar communications between the stomach and intestines.

Clinical Study

Of the 20 patients with gastroenterocolic fistula 12 developed the fistula following operation for benign peptic ulcer. In 5 the fistula developed as a result of carcinoma. Two patients acquired fistulae as a result of perforation of a diverticulum of the colon. One was a duodenocolic communication and the other ileocolic. The twentieth patient had an ileocolic fistula of undetermined origin, but this was thought to be the probable result of perforated diverticulum of the colon. The 12 patients who developed fistula after operation for peptic ulcer were all men, their ages ranging from 37 to 57 years. In 9 patients the site of the primary ulcer was the duodenum, and in 3 instances the site of the primary lesion could not be determined from the available records.

In 8 of the 12 patients the primary operation was posterior gastroenterostomy. One had an anterior gastroenterostomy. It is significant that 1 patient had partial gastric resection. The types of operation upon 2 patients could not be determined from the records. The fistulae developed from two to twenty years after the original operation. Hollander and Mage[21] state that complications of surgical treatment of peptic ulcer usually develop within one to five years after operation and rarely after ten years. In our series 6 of the 12 fistulae developed twelve or more years after the initial operation, and symptoms of the syndrome had been present from three months to five years.

The outstanding symptoms were diarrhea and loss of weight and strength. Diarrhea was the chief complaint in 11 of the 12 patients. One patient complained of persistent constipation. When diarrhea was present the stools were watery, foamy, and foul, but not voluminous. The number varied from three to fourteen stools daily. With but one exception the patients did not note undigested food in the stools. Diarrhea was usually the first symptom, and the associated symptoms of loss of

weight, avitaminosis, edema, and other features developed after diarrhea had become persistent. Eleven of the 12 patients had weight loss which varied from 5 to 50 pounds. Seven of these patients complained of marked loss of strength in association with loss of weight. Four patients complained specifically of foul or fecal odor to the breath, usually associated with belching or vomiting. Appetite, even in the presence of fecal odor to the breath, usually remained good. One patient stated that his appetite was excessive despite "constant fecal breath" and continuous weight loss.

The objective manifestations observed in the 12 patients with gastrocolic fistula following operation for benign peptic ulcer varied with the severity of the symptoms. In the early phase of an illness without remissions or in an illness of long duration but with intermittent symptoms the patient appeared to be in reasonably good health. In the more severe or advanced phases the patient appeared emaciated, dehydrated, and desperately ill. There were signs of multiple vitamin deficiency including night blindness, paresthesia, peripheral neuritis, cheilosis, glossitis, conjunctivitis, pellagra, achymosis, and tetany.

Biophotometer tests were done on 3 of our patients. Two had distinctly abnormal curves, while the third was within normal limits, although the patient complained of blurred vision for a period of one month prior to admission. Prothrombin time was measured in 2 patients and found to be normal. Isolated blood sugar determinations were normal. Two patients had glucose tolerance studies, and 1 revealed a dysinsulin type curve. Four of 12 patients had blood protein examinations, and all were below normal. Only 3 patients had bromsulfalein liver function tests, and in 1, using 5 mg. dye per kilogram body weight, there was 36 per cent retention of dye at the end of thirty minutes. Two patients had blood calcium and phosphorus determinations. One was normal and one was abnormal. The latter revealed 8.4 mg. of calcium per 100 cc. of blood and 2.5 mg. phosphorus per 100 cc. of blood. This patient complained of pain in the skeletal structures of three months' duration preceding admission to the Clinic. Roentgenograms of the spine revealed decalcification. None of the patients who had peptic ulcer developed anacidity with the fistulae. Diarrhea was the major complaint of all patients, but only 6 had recorded stool examinations. All 6 had steatorrhea, but serial studies in 2 patients revealed steatorrhea to be inconstant. Eleven of the 12 patients had blood examinations, 6 of which were normal. Four patients had normocytic hypochromic anemia, and one had anemia of an undetermined type. In several instances the patient had received liver and/or iron for anemia prior to admission to the Clinic.

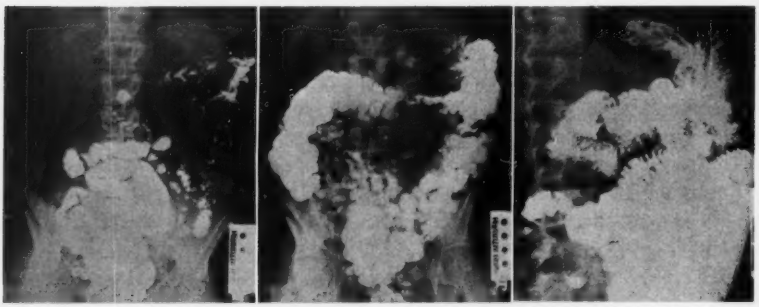

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FIG. 1. Flow of barium meal in patient with gastrocolic fistula. Demonstrates regurgitation of colonic contents into stomach through fistula. (a) Two hours after meal. Barium fills upper intestine. (b) Five hours after meal. Stomach is empty. Barium is scattered throughout small intestine. Small traces of barium are in distal transverse and descending colon. This probably entered the colon directly from stomach. (c) Twenty-four hours after meal. Considerable barium remains in small intestine and colon, but there is more barium in stomach than at end of five hours, indicating regurgitation from colon through fistula into stomach.

A review of the roentgenologic material revealed that 8 patients who had developed fistulae following operation for peptic ulcer had sufficient evidence for analyses of direction of the flow of barium, motility, and change in small bowel pattern. Because we were concerned primarily with the direction of flow of aliment, 2 other patients with sufficient evidence for analysis of direction of flow are included in the discussion of the roentgenologic findings, although these 2 patients had fistulae as a result of carcinoma of the stomach which had perforated into the colon. Finally, the roentgenograms of 1 case observed elsewhere* are included in this part of the discussion because they demonstrated the phenomenon which we were able to observe in dogs with gastrocolic anastomoses and were not able to observe in our series of human patients (fig. 1).

In our analysis of the direction of the flow, orally ingested barium always passed through the pylorus or into the small intestine and thence into the colon through the ileocecal valve (fig. 2). The colonic fistula was shown in only 2 patients using the barium meal but was demonstrated in all 11 by administration of a barium enema. Furthermore, in 1 of the patients in whom much of the oral barium flowed through the fistula into the colon at one examination, at a later examination the entire aliment passed through the pylorus and did not enter the fistula (fig. 3). In most instances the stomach emptied rapidly, and the head of the meal progressed rapidly through the small intestine. However, it

*This patient was under the care of Dr. Leo Hardt, Chicago.

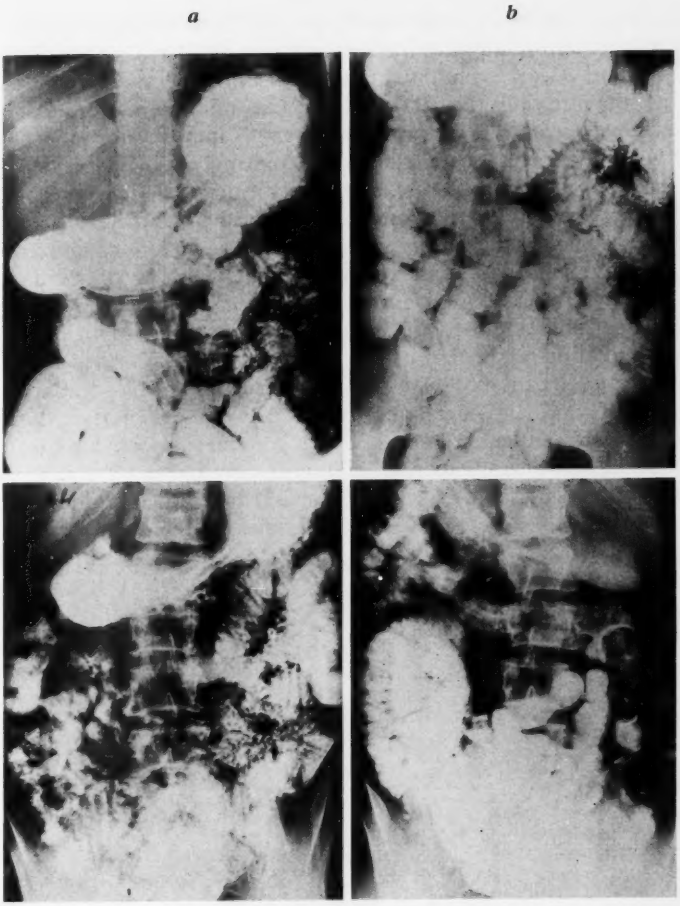

FIG. 2. Flow of barium meal in patient with gastrocolic fistula. (a) Fifteen minutes after meal. Stomach is well filled. Considerable barium has passed through pylorus, and only a trace outlines gastrocolic stoma. (b) One-half hour after meal. Barium is scattered through small intestine, but none has passed ileocecal valve. There is no apparent increase of barium entering transverse colon through fistula. (c) One and one-half hours after meal. Stomach still contains considerable barium. Head of meal has reached hepatic flexure, but bulk of meal is scattered through small intestine or remains in stomach. Still only a very small part of meal has passed through fistula. (d) Three and one-quarter hours after meal. Small amount of barium remains in stomach. Head of meal has reached splenic flexure, but bulk of meal still remains scattered throughout small intestine.

is significant that serial observation revealed barium scattered throughout the large and small intestine for long periods after the administration of a barium meal, even though the barium *head* progressed rapidly through the intestines (fig. 2). Similarly, barium administered by enema was observed scattered throughout the small intestine for long periods after regurgitation into the stomach. Abnormalities in pattern of the mucosa of the small intestine, commonly called "deficiency state" or "deficiency pattern", were found in 6 of the 11 patients.

Microscopic study of tissue was limited to specimens of stomach and intestine from the region of the fistula. In 2 instances chronic inflammation of the jejunal and gastric mucosa was recorded.

The treatment advised in the series of 12 patients with fistula following operation for benign peptic ulcer was reoperation for correction of the fistula. Eight of the 12 patients had corrective operations at Cleveland Clinic, and there were no operative or hospital deaths. The preoperative treatment consisted of such general supportive measures as low residue diet, supplemental oral and parenteral vitamins, whole blood transfusions, and the use of the intravenous and subcutaneous saline dextrose solutions. Protein hydrolysates, sulfonamides, or penicil-

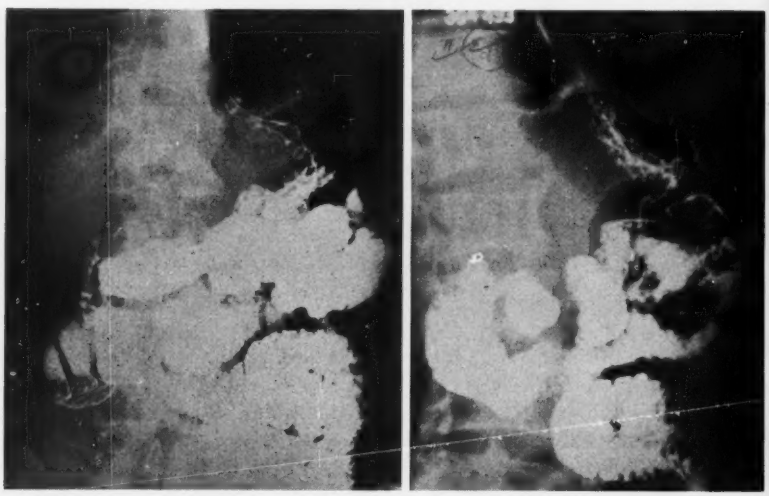

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FIG. 3. Flow of barium meal in patient with gastrocolic fistula. (a) During one examination some barium passed directly from stomach to colon through fistula, although considerable amount also passed through pylorus into small intestine at the same time. (b) At a later examination of same patient only a very small part of meal passed through the fistula, while nearly all passed through the pylorus.

lin were not available for the patients operated upon in earlier years, and the illness of those operated upon in recent years was not of sufficient gravity to require use of the drugs.

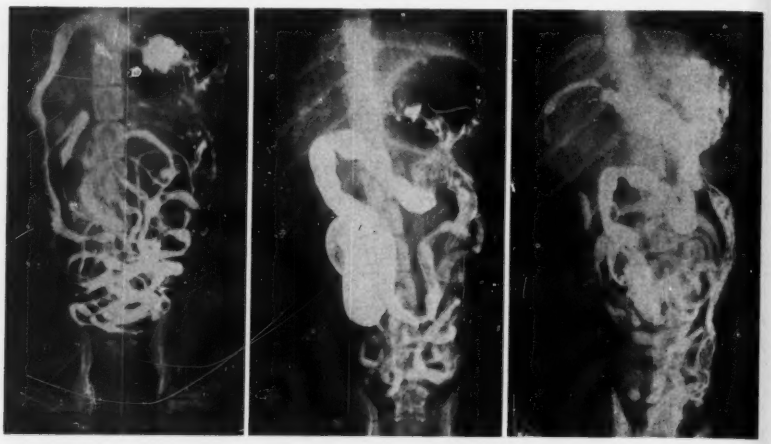
Experimental Study

Experiments on 7 dogs are the basis for this part of the report, although additional dogs with various types of operations are under observation. All animals were kept on a standard diet of Purina Chow Dog Food, supplemented twice weekly with one-half pound of ground horse meat. During the preoperative control period observations were made on weight, appetite, general behavior, blood count, stools, and roentgenologic appearance of the gastrointestinal tract.

Four dogs had gastrocolic fistulae, 1 had an anterior gastrojejunocolic fistula, 1 had a posterior gastrojejunocolic anastomosis, and 1 had a duodenocolic communication. In all but 1 the artificial stoma was 3 to 4 cm. in diameter. The last dog had a gastrocolic fistula with a stoma only 1 cm. in diameter and one year after operation has not developed the syndrome.

After operation the dogs appeared to pass through four stages of the syndrome when the stoma was large enough for the syndrome to develop. They remained healthy for three to nine months postoperatively. The smaller the stoma the longer time required for development of the syndrome, as evidenced by the 1 dog with a 1 cm. fistula. After this first stage, which might be called the "latent period", the second stage developed. It was characterized by weight loss and microcytic normochromic anemia. The third phase included intermittent diarrhea and steatorrhea, more marked anemia, and early inflammatory changes in the gastrointestinal tract. The fourth or last stage was characterized by persistent diarrhea and steatorrhea, severe malnutrition, striking inflammation with some ulcerative changes in the gastrointestinal tract, and progression of anemia. In 2 dogs the anemia became definitely macrocytic hyperchromic.

Diarrhea developed in all but 1 dog (the animal with 1 cm. stoma). The fistula in this animal was "functionally closed", but under slight pressure part of a barium enema passed through the fistula into the stomach. (Postmortem examination sixteen months after operation revealed a valve-like flap of tissue which during life prevented flow of material either way.) Diarrhea was intermittent in the earlier stage of the syndrome. Stools were light in color, watery, and foul. Steatorrhea was demonstrated in 5 dogs. The severity of steatorrhea corresponded to the severity of diarrhea.



a *b* *c*

FIG. 4. Flow of barium meal in dog with gastrocolic anastomosis 4 cm. in diameter. (a) Fifteen minutes after meal. Barium is passing through pylorus. Duodenum is well-filled, and barium is scattered through normal small intestine. (b) One and one-half hours after meal. Head of meal is in transverse colon, but large amount remains in small intestine. Fistula is faintly outlined, and small amount of barium dimly outlines descending colon. Stomach is almost empty. (c) Three and one-half hours after meal. Considerable barium remains in small intestine, but portion of colon shown filled in 4(b) is partly empty, and the stomach contains much more barium. Colonic contents have been regurgitated into stomach.

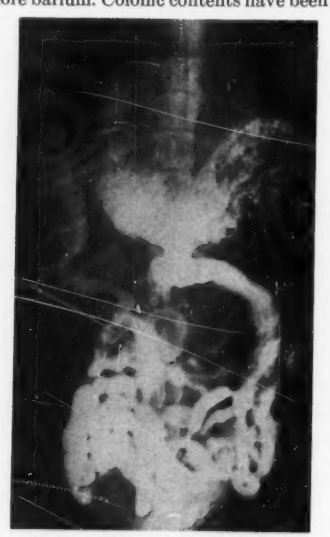


FIG. 5. Flow of barium meal in dog with gastrocolic fistula 4 cm. in diameter. Much of meal has passed directly into colon, although at the same time considerable amount has passed through pylorus.

All but 2 dogs had ravenous appetites throughout their illness. The measured amount of food ingested by the 2 dogs without ravenous appetites was still adequate to maintain normal nutrition. Yet in the third and fourth stages of the syndrome all dogs developed malnutrition, loss of weight, dehydration, conjunctivitis, xerophthalmia, glossitis, dry atrophic tongue, and roughing of coat with patchy loss of hair. Thus the dogs developed a syndrome comparable to that in human beings with gastrocolic fistula.

Roentgenologic studies revealed that orally administered barium always passed through the pylorus or stoma into the upper small intestine and from the small intestine through the ileocecal valve into the cecum (fig. 4). However, the amount which went this way was variable. In 3 dogs the entire barium meal left the stomach through the pylorus. In 4 dogs the barium entered the small and large intestine simultaneously through the pylorus and the fistula. However, in 3 of these 4 dogs almost the entire meal passed through the pylorus, while in only 1 dog did the amount leaving through the fistula equal that going through the pylorus. The latter dog passed a stool containing barium one-half hour after administration of the meal, but considerable barium remained in the small intestine two and one-half hours later (fig. 5). Another examination of this same dog at a later date revealed that the entire meal advanced into the small intestine, and none entered the colon through the fistula.

Regurgitation of orally administered barium from the colon into the stomach was observed in 2 dogs. In one instance it was observed during fluoroscopy (fig. 4) and once during gastroscopy.

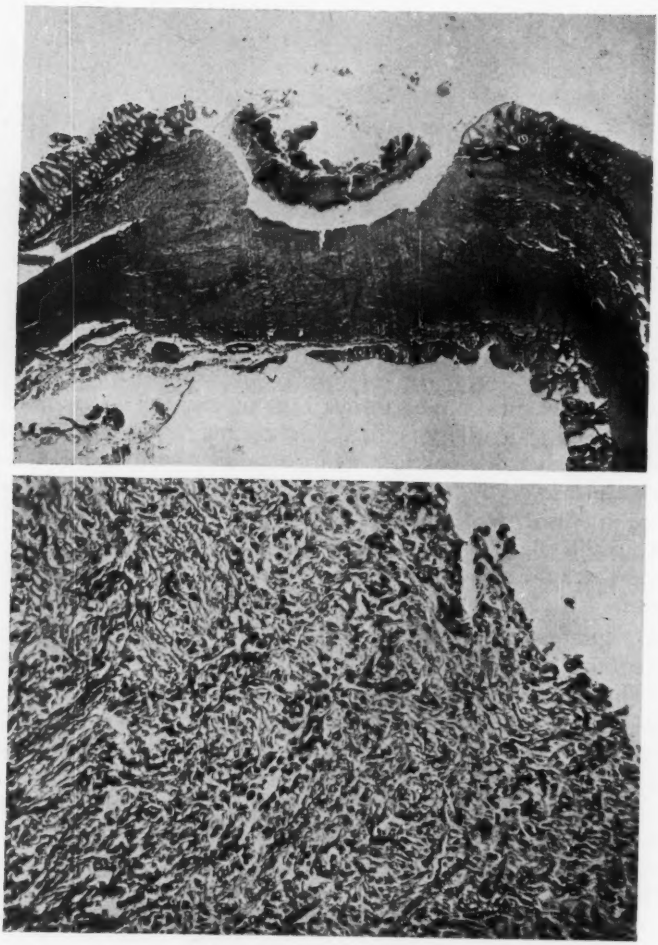
Fourteen dogs were studied to observe the "normal" small bowel pattern. After operation the only change associated with malnutrition and hypoproteinemia which we could observe was dilatation of the intestine. Segmentation, "puddling" of barium, and other signs observed in human patients and described as "deficiency patterns" were not seen in the dogs. There was suggestive evidence of hypomotility in these animals.

Two dogs were observed by gastroscopy. In both animals there was catarrhal inflammation of the stomach. In 1 dog, stool coming through the fistula into the stomach was observed.

Pathology

Six dogs had postmortem studies. In 5 instances the gastroenteric or gastrocolic stoma measured 3 to 4 cm. in diameter, the other one measuring only 1 cm. and having a valve-like flap of tissue covering

a



b

FIG. 6. Gastric ulcer in dog with gastrocolic anastomosis. (a) Low power. (b) High power shows evidence of chronicity and organization.

the stoma. The changes in the stomach of those animals which died or were killed in the early phase of their illness varied from normal to mild catarrhal or such superficial inflammation. Two dogs whose illness was more prolonged developed gastric ulcers (fig. 6). The surface layer of

the ulceration consisted of necrotic tissue and exudate. The latter consisted of lymphocytes, polymorphonuclear leukocytes, and occasional plasma cells. Under the surface layer there was a layer of organization showing fibroblastic proliferation with young blood vessels and infiltrated with lymphocytes and a few polymorphonuclear leukocytes. The inflammatory changes extended into and partly involved the muscularis. The rest of the stomach showed little change.

In the small intestine there was diffuse patchy hyperemia of the small intestine. It was more marked in the duodenum and upper jejunum, becoming less severe in the lower portion of the small intestine. The colon showed no change. In the small intestine the changes were limited to the papillae where there was a striking increase in the cellular elements (fig. 7). The inflammatory infiltration consisted of lymphocytes and plasma cells, a subacute to chronic type of change limited almost exclusively to the mucosa. There was some fibrosis of the tunica propria of the mucosa in the papillae.

Summary

1. A review of the literature reveals conflicting opinions regarding the mechanism which produces the syndrome following development of gastrocolic fistula.

2. The outstanding symptom was diarrhea, although 1 of 20 patients had constipation. Diarrhea might be intermittent, especially in the early stages of illness.

3. Steatorrhea roughly paralleled diarrhea in frequency and intensity.

4. Weight loss, polyavitaminosis, and malnutrition developed after diarrhea and steatorrhea had become fairly constant.

5. Eleven of 20 patients had roentgenologic studies sufficient for detailed study. In all 11 patients barium passed from the stomach into the upper small intestine, but in only 2 instances did barium pass from the stomach into the colon through the fistula.

6. In all 11 patients the fistula was demonstrated roentgenologically by administration of a barium enema.

7. The *head* of the barium meal passed rapidly through the small intestine, but for long periods after administration barium remained scattered through the small intestine. Similarly, barium which regurgitated into the stomach after being administered by enema remained scattered throughout the small intestine for long periods afterward.

8. In 1 patient with gastrojejunocolic fistula the barium meal passed through the pylorus and the fistula. Twenty-four hours later most of the barium was still scattered through the small intestine and colon.

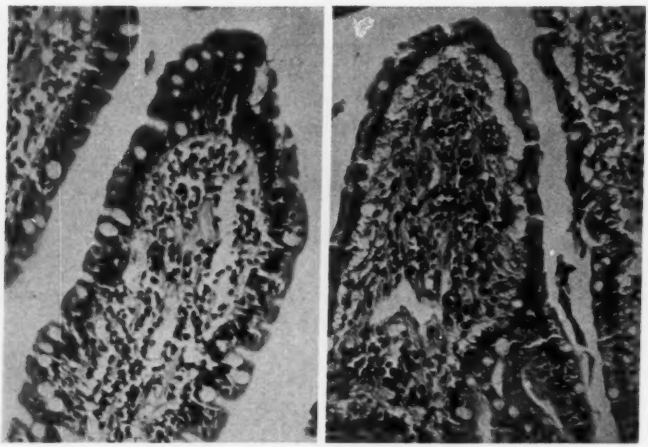


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FIG. 7. Small intestine of dog with gastrocolic anastomosis 4 cm. in diameter. (a) Typical normal papilla before making gastrocolic anastomosis. (b) After anastomosis and after development of syndrome there is a striking increase in cellular elements. The inflammatory reaction is a subacute to chronic type limited almost exclusively to mucosa.

The stomach contained more barium at the end of twenty-four hours than at the end of five hours, indicating regurgitation through the fistula into the stomach.

9. Five dogs which were killed during the course of the syndrome, or which died as a result of the syndrome, showed inflammatory changes in the stomach. Two dogs showed gastric ulceration with evidence of organization and some degree of chronicity. In the small intestine, especially the upper third, there was a striking subacute to chronic type of inflammatory infiltration limited almost exclusively to the mucosa of the papillae.

10. The development of anemia presented an interesting observation and warrants further study. It is suggested, although our studies were inadequate, that the development of anemia follows a definite pattern. The first change is to hypochromic microcytic anemia in the earlier phases of illness. If the animal is not too sick and survives long enough, the anemia tends to become macrocytic hyperchromic.

Conclusions

Tentative conclusions based on the above evidence and observations of others are: [2,6,7,8,11]

1. Sufficient aliment to maintain adequate nutrition passes from the stomach into the upper small intestine.

2. Passage of aliment directly from the stomach into the colon is not frequent enough nor in large enough amounts to cause the syndrome.

3. Deranged digestive and absorptive functions of the small intestine cause the syndrome.

4. Colonic contents regurgitate through the fistula into the stomach.

5. Derangement of small intestine function is probably the result of damage to the intestinal mucosa caused by the passage of colonic contents through the small intestine.

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SKELETAL CHANGES IN CHRONIC FLUORINE INTOXICATION

Report of a Case

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Although the bone changes of chronic fluorine intoxication in man have been well described abroad,[1] the American literature contains only a single case report[2] concerning the occurrence of these changes in workers in this country who have been exposed to fluorine compounds over long periods of time. It therefore seemed desirable to record a recent case in which a man who had handled various fluorides regularly throughout a period of thirty years' employment in a chemical plant presented the characteristic roentgenologic features of extensive deposition of fluoride in the skeleton.

Report of a Case

A white man, aged 58 years, had felt well until three months before his first visit to the Clinic when he noted the onset of fatigue and dyspnea on exertion. The symptoms had gradually become more troublesome, and during the three weeks preceding his admission there had been occasional moderately severe frontal headaches. There were no other complaints. Since 1916 the patient had been steadily employed in a chemical plant where his work involved the constant handling of fluorine salts, chiefly sodium fluoride. According to his statement there was considerable chemical dust in the air of the room in which he worked, and although he was supplied with a protective mask he often dispensed with its use for the sake of comfort.

Physical examination revealed a well developed, well nourished man in no respiratory discomfort. The temperature was normal, the pulse rate 52 per minute, and the blood pressure 110/70. There was no cyanosis, and the peripheral venous pressure was not elevated. The few remaining teeth showed a brownish staining, but there was no mottling of the enamel. The anteroposterior diameter of the thorax was increased, and the inspiratory expansion of the chest was greatly limited. The lungs were hyperresonant on percussion, and no rales were heard. The heart was not enlarged, and its rhythm was regular. The heart sounds were somewhat distant but otherwise normal. No murmurs were present. The peripheral arteries showed only early diffuse thickening. Abdominal, rectal, and neurologic examination revealed nothing abnormal.

The urine had a specific gravity of 1.020 and contained no albumin, sugar, or abnormal cellular elements. The red blood cell count was 4,980,000, and the hemoglobin content of the blood 13.5 Gm. (88 per cent). The leukocyte count was 7100 with a normal differential count and no abnormal white cell forms. Platelets appeared to be present in normal numbers. Considerable difficulty was experienced in performing a sternal marrow puncture because of the hardness of the cortex of the bone. Examination of the aspirated marrow, however, revealed no abnormal changes. The calcium content of the blood serum was 10 mg. per 100 cc., and the phosphorus content 3.3 mg. The alkaline

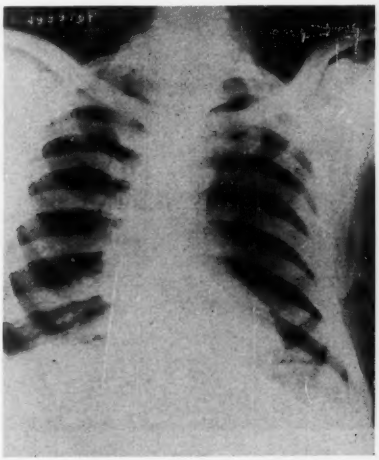

FIG. 1. Roentgenogram of the thorax. Illustrating the changes in the ribs, clavicles, scapula, and cervical region of the spine.

phosphatase activity of the serum was 4.9 units (normal 2 to 5 units), and the acid phosphatase 0.7 units (normal 0.1 to 1.0 units). The Wassermann reaction of the blood was negative. The electrocardiogram showed no diagnostic changes.

Roentgenograms of the thorax (fig. 1) revealed a striking increase in the opaqueness of the ribs, clavicles, scapulae, and dorsal vertebrae. Because of this finding films of other parts of the skeleton also were made and revealed similar changes involving the basilar bones of the skull, the mandible and maxilla, cervical region of the spine, lumbar region of the spine, pelvic bones, and the bones of the upper and lower extremities (figs. 2, 3, 4). The involvement of the vertebrae, ribs, and pelvic bones was essentially uniform in character and of such marked degree that the details of bone structure were almost completely obscured. The changes in the femurs and bones of the leg were somewhat less advanced, while the bones of the forearm showed still less involvement. Only relatively slight changes were present in the temporal, parietal, and occipital bones. In addition to the increase in density the bones showing the more advanced changes also appeared to be of increased breadth with thickening of the cortex, encroachment on the medullary cavity, and a somewhat irregular and indistinct cortical margin. The normal trabeculations were obliterated in the cancellous portions of these bones. No areas of bone destruction were present. The large joints showed no abnormalities, and the intervertebral cartilages appeared normal. There was no calcification of the costal cartilages.

Discussion

The two known manifestations of chronic fluorine intoxication in man are brownish discoloration and mottling of the teeth and roentgenologic changes in bone. The dental defects are encountered in individuals who, during the period of enamel formation of the permanent teeth, have lived in areas where the drinking water contains considerable

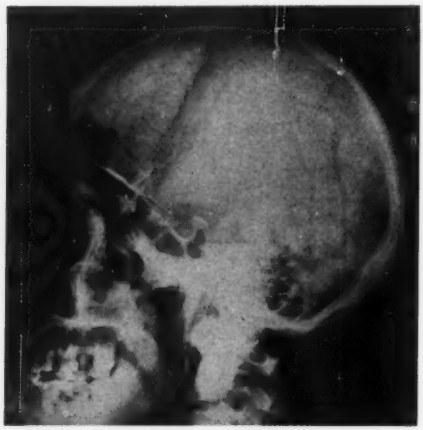

Fig. 2. Roentgenogram of the skull. Extensive changes in the cervical region of the spine mandible, maxilla, and bones of the base of the skull.

amounts of fluorine. The roentgenologic changes in bone were first described by Moller and Gudjonsson[1] in cryolite* workers in Denmark. These investigators were unable to demonstrate similar changes in individuals exposed to the inhalation of fluorine fumes in glass, enamel, and sulfuric acid industries and therefore concluded that the findings in the cryolite workers were the result of ingestion, not inhalation, of small amounts of fluorides over long periods of time. The case reported by Bishop[2] occurred in a man who had been employed for eighteen years in a fertilizer factory where he handled finely ground rock phosphate containing 4 per cent fluorine. Necropsy studies in this patient revealed increased hardness of the involved bones with thickening of the cortex and encroachment on the marrow cavity. Although only a small amount of marrow tissue remained in the ribs, it appeared to be of normal structure. This is in harmony with the observations on the aspirated bone marrow in the present case.

Wolff and Kerr[3] made chemical analyses of the involved bones in Bishop's case and reported that the fluorine content was increased up to twenty times the normal value, the highest concentration being found in the vertebrae and the lowest in the long bones. They also described the external surfaces of the bones as being covered with chalky white areas, nodular and plate-like exostoses, and osteophytes. The specific gravity of the bones was found to be abnormally low, however, and they

*Cryolite is a fluoride of aluminum and sodium which contains as much as 54 per cent of fluorine.

therefore concluded that the increased opacity to roentgen rays was due to increased thickness of the bones and not to an increase in actual density. No histologic studies were made. In 1891, however, Brandl and Tappeiner,[4] working on experimental fluoride poisoning in animals, reported that the bone structure was intact but the haversian canals were almost filled with crystals of calcium fluoride. This observation is difficult to reconcile with a reduced rather than an increased specific gravity of bone and indicates a need for further investigation.

Chronic fluoride intoxication in man causes no detectable impairment of general health provided the concentration of fluoride in the ingested dust is not too great. Nausea and vomiting were common complaints, however, in the cryolite workers studied by Moller and Gudjonsson,[1] the symptoms apparently being due to gastric irritation. In the present case there was no evidence that fluoride intoxication was responsible for the patient's symptoms. The dyspnea and fatigue could be explained adequately as due to emphysema of the lungs. Whether the relative immobility of the thoracic cage was the result of the changes in the bones and was in turn responsible for the development of emphysema is strictly conjectural.

Summary

A case is reported in which a man who had handled various fluorides regularly throughout a period of thirty years' employment in a chemical

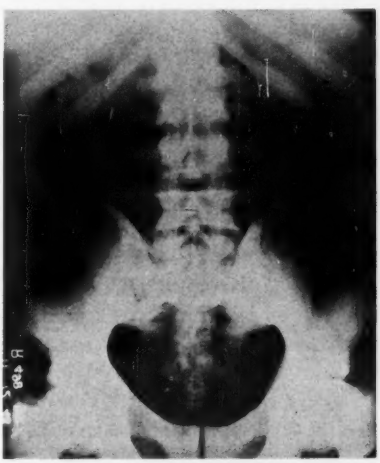

FIG. 3. Roentgenogram of the lumbar region of the spine and pelvis.

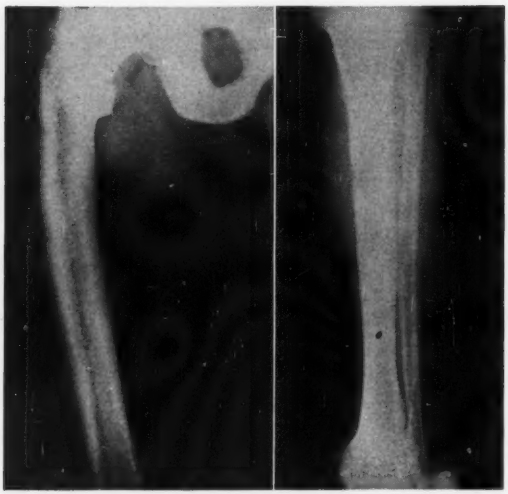

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Fig. 4. (a) Roentgenogram of the right femur, ischium, and pubis. (b) Roentgenogram of the right tibia and fibula.

plant presented the characteristic roentgenologic features of deposition of calcium fluoride in practically all of the bones of the skeleton. The principal changes consisted of a striking increase in opaqueness of the bones together with some increase in their breadth. The most advanced changes were present in the vertebrae, ribs, and pelvic bones. There was no anemia, and examination of the sternal bone marrow revealed no diagnostic changes. The calcium and phosphorus contents of the blood serum were within normal limits, and the phosphatase activity also was normal.

The patient had no symptoms that could be attributed directly to chronic fluorine intoxication, although one might speculate as to whether the changes in the bones of the thorax had favored the development of emphysema of the lungs.

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DIFFERENTIAL DIAGNOSIS BETWEEN CEREBRAL AND CEREBELLAR DEGENERATION AND BRAIN TUMOR

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The clinical picture of a brain tumor and a degenerative process in the brain is often similar, and the manifestations of these two pathologic states which progress slowly or intermittently make a differential diagnosis difficult.

During the last eight years at the Neurological Institute of New York, at the University Hospital of Baltimore, and the Cleveland Clinic a relatively large number of patients have been seen who were suspected of having a brain tumor but were shown to have atrophic disease of the brain by pneumo-encephalography or craniotomy. Fifty-two of these cases of cerebral and cerebellar atrophy were selected for a study to determine possible differences in the signs and symptoms of brain tumor and brain atrophy.

In these selected cases the average age was 33 with the youngest 17 and the oldest 47. In all cases hypertension, arteriosclerosis, toxic factors, trauma, and birth injury were ruled out as well as possible by detailed histories and examinations. The patients did not fit into the clinical picture of Pick's disease, Alzheimer's disease, or other clearly defined brain atrophies. There have been reported, however, cases of pseudo-sclerosis and of multiple sclerosis which clinically had certain resemblances to the patients in our series.

The average duration of symptoms before pneumo-encephalography or craniotomy was two and one-quarter years. The course of the disease in the great majority of the patients was slowly progressive, but there were several instances of fluctuation or an apparent arrest or improvement in the signs and symptoms. Many of the patients were followed over two years, while the longest follow-up was ten years.

The chief presenting symptoms were convulsive seizures and headache. Weakness of one side of the body, blurred vision, difficulty in saying words or in understanding words, loss of memory, lack of ability to concentrate, and staggering gait also were listed as complaints. On examination the most consistent finding was an increased excitability of the tendon reflexes on one side of the body. The following charts will present the principal symptoms and signs.

Symptoms

Headache	21	*Convulsions*	27
Localized	11	Generalized	15
Generalized	10	Jacksonian features	12

Weakness on one side of the body	17
Mental symptoms	14
Numbness on one side of the body	10
Aphasia, motor or sensory	6
Blurred vision	6
Double vision	3

Signs

Hyperreflexia on one side of the body	40
Hemiparesis or hemiplegia	22
Visual field defect	11
Ataxia, clumsiness, or staggering gait	11
Hypesthesia on one side of the body	10
Blurred disks or edema of the disk	8
Cranial nerve palsy	6
Unequal pupils	4
Primary optic atrophy	3

The tentative diagnosis in these cases was most often a tumor in the motor or premotor area. Parasagittal meningioma was considered in 14 cases.

The pneumo-encephalograms were extremely interesting. In two instances the diagnosis of brain tumor was actually more convincing after air studies when a definite ventricular shift was observed. However, nothing more than an atrophic process was found at the time of the craniotomy. In 26 cases the films showed changes consistent with atrophy of the right or left cerebral hemisphere. In 24 cases the atrophy was diffuse. In both groups there was either ventricular dilatation or marked increase of cortical markings or both.

The accompanying plates show typical examples of the encephalographic pictures (figs. 1, 2, 3, 4).

In the 17 cases which had complete removal of the fluid at encephalography the volume of fluid removed was greater than 160 cc. The greatest amount of fluid obtained was 338 cc. It was arbitrarily assumed that the average amount of spinal fluid in a normal healthy adult of 30 years of age was between 110 and 140 cc.

The spinal fluid pressure was below 150 mm. of water in all cases, and the spinal fluid protein was below 60 mg. in every case.

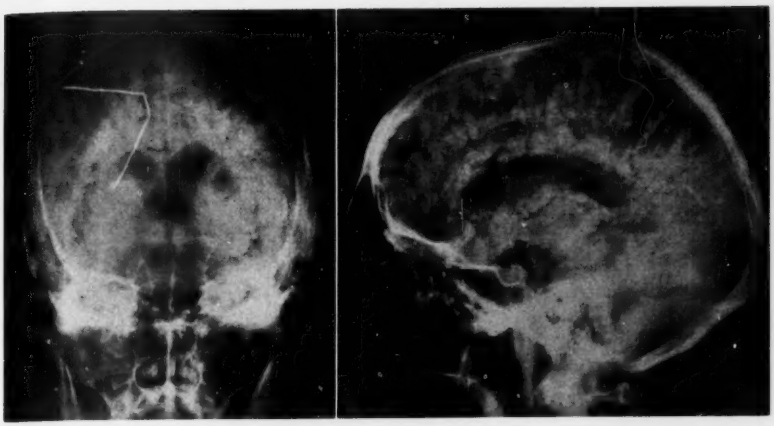

FIG. 1. Anteroposterior and lateral views showing dilatation of the lateral ventricles, more marked on the left. Increased cortical markings are visualized.

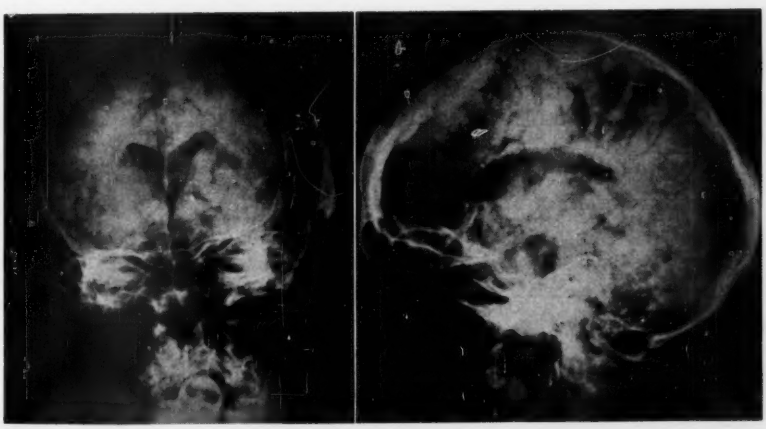

FIG. 2. Anteroposterior and lateral views showing minimal enlargement of the lateral ventricles with localized increase of cortical markings. Patient complained of Jacksonian convulsions of sensory type.

Electro-encephalograms were obtained in 18 cases. Thirteen of these showed evidence of a localized lesion usually corresponding to the clinical localization. In 4 cases a diffuse dysrhythmia was found and in 1 case a normal reading was recorded.

Discussion of Signs and Symptoms

Headache

Of the 21 patients who complained of headache, 11 localized the pain on one side of the head. This was usually to the side of the greatest atrophy, a localization which is occasionally found in posttraumatic degenerative disease of the brain. Of the 3 cases of cerebellar atrophy 2 had suboccipital headache. In our experience the headache of brain tumor is not as frequently referred to one side as it is in this type of brain atrophy.

Another interesting feature of the pain was the marked or moderate relief experienced by the patient upon lying down; in this sense it simulated the headache after spinal puncture, sometimes called the hypotensive headache. This headache is considered to be caused by a decreased cerebrospinal fluid pressure as recorded by the manometer, but in the cases selected no low spinal fluid pressures were recorded. The pain was described as dull or throbbing and in over 50 per cent of the cases as a severe pressure sensation associated with pain. In 3 cases the headache was improved after pneumo-encephalography and in 1 case was entirely relieved. In contradistinction to this, the headache of brain tumor is occasionally increased by the prone position and is rarely improved by pneumo-encephalography. In the atrophic diseases as well as in brain tumor the pain is increased by exertion. Excitement, nervousness or emotional strain is likely to increase the headache of brain atrophy to a greater degree than that of brain tumor.

In some cases of brain atrophy the headache tended to have a periodicity, lasting two to four hours and recurring at fairly regular intervals. The headache was rarely nocturnal.

Mental symptoms and signs

Of the strictly mental symptoms, loss of recent memory was the most commonly encountered. In the patients who were seen within a year or two after the onset of symptoms there was often found a depressed emotional state, of which the patient and his family or friends were clearly aware. The patients had a relatively keen insight into their disabilities and there was rarely a dulling of the whole sensorium as was

found in the infiltrating gliomas. These patients with atrophic brain disease appeared more fully aware of their surroundings than the tumor cases did, and their perceptive integration of ideas had a clarity and sensitivity that was not often found in patients with brain tumors. It is possible that in the atrophic diseases, an explanation for this lies in a selective degeneration of certain cortical layers or pathways.

Convulsions

In the majority of cases the convulsive seizure was not distinguishable from that occurring in brain tumor. There was, however, a fairly high proportion of cases with distinct reference of the convulsions to one side, and in many cases Jacksonian components were observed. The convulsions were often less severe and less frequent or disappeared entirely after pneumo-encephalography.

Hemiparesis and hemihypesthesia

The complaint of weakness or numbness on one side of the body was found in 27 cases and in the majority of these this symptom assumed a progressive course. On the other hand in some cases a story of remission of symptoms could be obtained and in a few instances in the early stages of the disease there were acute temporary exacerbations which suggested multiple sclerosis, a vasospastic or occlusive vascular process. Remissions in patients with brain tumors were relatively rare.

The other feature that we observed was that the degree of weakness or numbness described by the patient was rarely confirmed by examination. The patient felt that the numbness was far greater than could be actually demonstrated objectively. This was brought out by giving the patient a coin with his eyes closed and asking him to name the object and then the denomination. If the coin was placed in the affected hand he usually started immediately to feel it with the normal hand. If he was prevented from doing this, he would name the coin correctly by feeling it with the affected hand. On questioning he would say, "I didn't think I could name it with my bad hand" or "I always use my good hand to feel things." If the patient was not sure of loss of sensation it was found that when the right and left side of the body were stimulated simultaneously the patient in many cases would state immediately that the stimulus was less well perceived on the affected side.

On the motor side examination often showed varying degrees of loss of strength in the affected lower extremity, and this was associated with an increase of deep reflexes. The interesting feature, however, was the surprisingly high percentage (over 75 per cent) of cases of paresis of

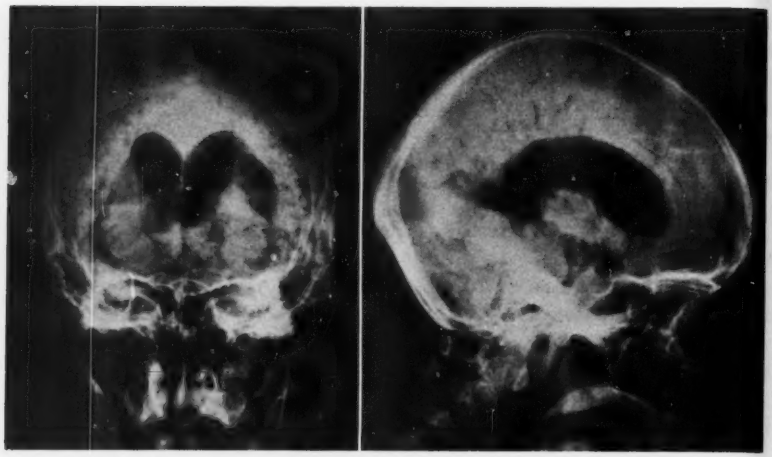

FIG. 3. Anteroposterior and lateral views revealing marked dilatation of the lateral ventricles with essentially normal cortical markings.

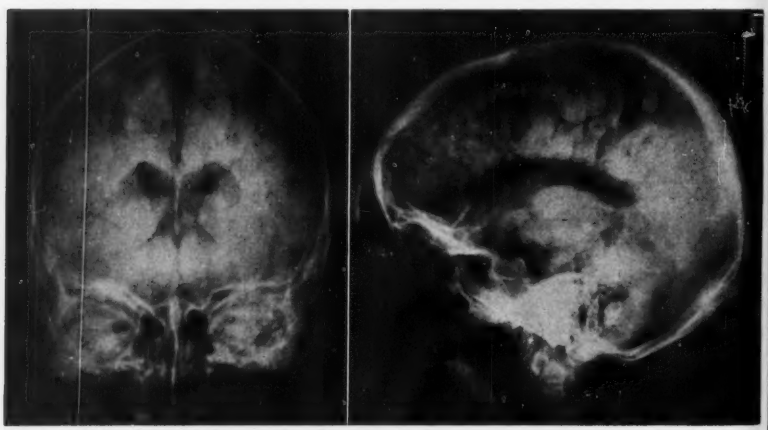

FIG. 4. Anteroposterior and lateral views showing diffuse increase of cortical markings and slight dilatation of the lateral ventricles.

the leg without a Babinski response or confirmatory responses such as are found in cases of brain tumor that involve the motor cortex or pyramidal tracts.

Discussion of Literature

The literature on brain atrophy is voluminous and no attempt will be made here to review it. Recently, an interesting paper on cortical atrophy was published in England that has a direct bearing on this report. Fleminger (1946)[1] described 28 cases of brain atrophy and discussed the differential diagnosis of brain tumor. Four of these patients had craniotomies and at operation "the cortex was shrunken and rubbery." There was microscopic evidence of cortical degeneration and sclerosis of unknown etiology, but in 2 cases it was observed that the greatest changes were in close proximity to the blood vessels. Seventy-five per cent of the cases of brain atrophy described by Jackson (1946)[1] had epilepsy, 25 per cent had a visual field defect and 50 per cent had headache of the hypotensive type.

Riley and Elsberg (1926)[2] and Gordon (1940)[3] emphasized in the differential diagnosis of brain tumor and brain atrophy that the symptoms and signs in the latter condition are often remittent or intermittent and that they may be referred to both cerebral hemispheres.

Fay in 1930[4] suggested that a hydraulic pressure mechanism might be responsible for the development of certain types of widespread atrophic degeneration of the brain in younger patients and in those without arteriosclerosis. He also presented encephalographic evidence to show that the frontal areas were involved most frequently and the anterior and upper part of the parietal region were next. In the majority of cases selected for this report the frontal and superior parietal regions were the areas of greatest predilection.

The occurrence of constriction of the peripheral vascular bed on the side of the body opposite the brain atrophy was stressed by Kerr and Underwood in 1936.[5] Vegetative disturbances of this nature were encountered by us when coldness of the extremities with vasomotor changes were found in 11 of our cases.

Summary

In the 52 cases a brain tumor was suspected because of the occurrence of headache, convulsions or localized central nervous system symptoms.

The differences and the similarities of the headache, convulsions, and neurologic findings in brain tumor and brain atrophy have been

discussed. It has been pointed out that in many instances patients with atrophic brain disease had a different type of headache, a greater preservation of the sensorium than in brain tumor. On examination of the sensory and motor systems in cases of brain atrophy, the objective findings were definitely less marked than were the subjective symptoms. The pneumo-encephalograms showed a diffuse or localized atrophy, and in some cases improvement of signs and symptoms followed air injection. In a few recent cases interruption of the sympathetic nervous system impulses to the brain produced by stellate ganglion blocks, stellate ganglionectomy, or upper thoracic anterior rhizotomy has been of measurable value, although it is too early to state with any certainty that there will be lasting beneficial effects.

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INTRA-ARTERIAL TRANSFUSION IN THE TREATMENT OF EXPERIMENTAL HEMORRHAGIC SHOCK

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Research Division

Experiments on the value of intra-arterial transfusion in the treatment of hemorrhagic shock were extended to an evaluation of the same method in extreme emergencies, including resuscitation. In a previous paper[1] we described the production of severe hemorrhagic shock in dogs and subsequent intra-arterial blood transfusion of the shocked animals. As a result of these experiments three criteria for prediction of the probable fate of the animals in shock were established: (1) persistently falling arterial pressure during the hypotensive period indicates small chance for survival; (2) the larger the intake of blood during arterial transfusion to establish normal pressure, the smaller the chance of survival; (3) the more nearly normal the pressor response to adrenalin after transfusion the better the chance of survival.

Method

The experimental technic for production of shock was described in the previous report. Suffice it to repeat here that the animal is bled rapidly from a femoral artery (fig. 1, A) until an arterial pressure of 50 mm. Hg is established. A canula (A) is connected through one branch with a mercury manometer (B) which permits recording the arterial pressure on a kymograph. The other branch leads to a bottle-reservoir (C) in which the withdrawn blood is stored under controlled pressure (hand pump, D; manometer, E; and sphygmomanometer, F). The 50 mm. Hg level of hypotension is maintained for ninety minutes, after which it is lowered to 30 mm. Hg by further withdrawal of blood. This 30 mm. Hg level is held for forty-five more minutes, making the total time of hypotension at least one hundred and thirty-five minutes. After the hypotensive period, all or part of the blood is reinfused through the same femoral artery. Kymographic records of arterial pressure, venous pressure (catheter, G, in jugular vein; connected to water manometer, H), weight of blood in reservoir (C), respiratory rate (pneumograph and tambour, K), and time intervals (M) of one minute were obtained for the duration of the entire experiment.

Mongrel dogs of an average weight of 11 kg. were used in these experiments. They were anesthetized by subcutaneous injection of 5

mg./kg. of morphine sulfate and intraperitoneal injection of 30 mg./kg. of sodium pentobarbital. In each experiment about 150 ml. of a saline solution containing 15 mg. of heparin was used as an anticoagulant in the reservoir and connecting tubes. In addition 0.3 mg./10 kg. of heparin was given intravenously before bleeding.

Criteria

The most valuable criterion for predicting the probable fate of the animal in deep hemorrhagic shock is the phenomenon of a persistently falling arterial pressure during the hypotensive period. This is especially so in the treatment of shock. A persistent drop of pressure may occur at practically any time; in some cases it begins within half an hour after bleeding, in others it may not occur for several hours. Only one of 52 animals survived permanently which were submitted to bleeding and kept at the reduced pressure for one hundred and thirty-five minutes, and in which the arterial pressure showed a persistent tendency to drop during this period. On the other hand, of 63 animals showing no such tendency during the hypotensive period, 47 (74 per cent) survived permanently after transfusion. In deep shock, a persistent tendency of

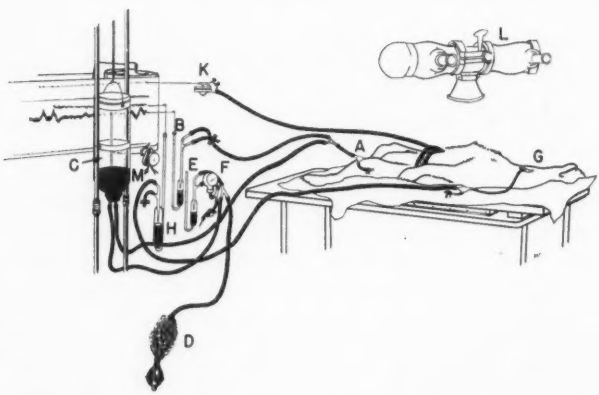

FIG. 1. Experimental bleeding and transfusion apparatus. A. Canula in femoral artery; B. Mercury manometer, recording arterial pressure on kymograph; C. Blood reservoir, connected with A, suspended on spiral spring and equipped with recording pen; D. Hand pump, connected to air tube in reservoir permitting regulation of air pressure in reservoir; E and F. Mercury manometer and sphygmomanometer for controlling air pressure in reservoir; G. Catheter in jugular vein; H. Water manometer, recording venous pressure on kymograph; K. Tambour connected with pneumograph, recording respiration rate on kymograph; L. X-ray tube; M. Timer, recording intervals of one minute.

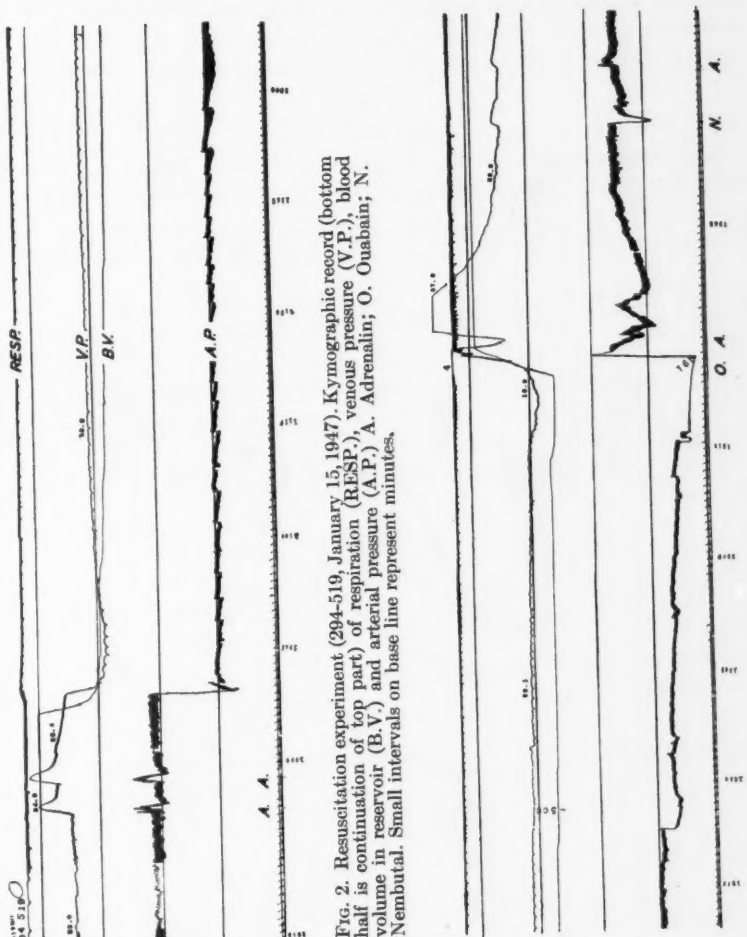

FIG. 2. Resuscitation experiment (294-519, January 15, 1947). Kymographic record (bottom half is continuation of top part) of respiration (RESP.), venous pressure (V.P.), blood volume in reservoir (B.V.) and arterial pressure (A.P.) A. Adrenalin; O. Ouabain; N. Nembutal. Small intervals on base line represent minutes.

arterial pressure to fall off must therefore be considered an emergency and the animal should be transfused at once if it is to be saved. Intra-arterial transfusion is indicated in such an emergency to restore normal arterial pressure and blood volume in the shortest possible time.

Resuscitation

To evaluate intra-arterial transfusions under extreme conditions in a group of 32 shocked animals, we continued withdrawing blood

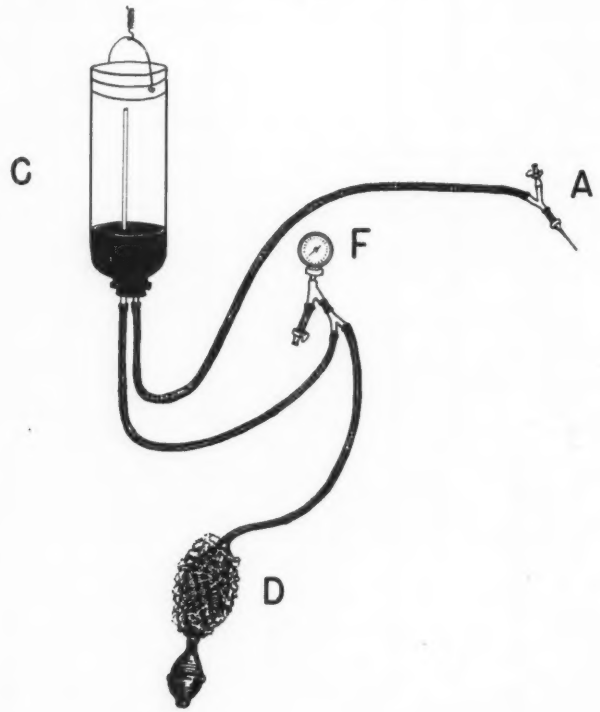

FIG. 3. Practical bleeding and transfusion apparatus. A. Needle for insertion into artery; C. Blood reservoir; D. Hand pump; F. Sphygmomanometer.

after the one hundred and thirty-five minute hypotensive period until circulation and respiration stopped completely, as indicated by electrocardiographic and pneumographic observations. Within two to five

minutes after stoppage the blood was reinfused arterially at a rapid rate, ouabain (0.05 mg./kg.) was given intravenously, 0.5 ml. of a 1:10,000 solution adrenalin intra-arterially, and artificial respiration was started.

Results

Of the 32 animals used in this group for resuscitation 9 (28 per cent) survived indefinitely, 18 (56 per cent) from one to thirty-six hours, with an average of eleven hours, and 5 (16 per cent) could not be resuscitated. Kymographic record of arterial and venous pressures, blood volume in reservoir, and respiration rate for such an experiment is presented in fig. 2.

Simplified Apparatus

A simplification of the original apparatus of Kohlstaedt and Page[2] for the experimental bleeding and transfusion (fig. 1) is shown in fig. 3. It contains only the essential parts and has no provision for permanent recordings. However, for practical purposes it lends itself well to bleeding, storage, or blood transfusion under controlled pressures.[3]

Summary

An apparatus is described for treatment of severe experimental hemorrhagic shock by intra-arterial transfusion. The value of this method is demonstrated in the treatment of dogs in hemorrhagic shock and in resuscitation of animals whose circulation and respiration has stopped for a period of several minutes.

The authors wish to express their appreciation to Betty May Evans and Barney Tautkins for their valuable help in these experiments.

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HYPOSPADIAS

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This congenital malformation of the urethra which occurs once in every 350 males, is found in various parts of the urethra and presents certain difficulties in obtaining a successful closure. Many of these patients are first seen as infants, and treatment is usually deferred until the child is 4 or 5 years of age. The urethral canal terminates at a site on the under surface of the penis rather than in its normal position at the tip of the glans. The urethra distal to the false opening is usually absent. The glandular portion having a separate origin is observed as a groove varying in size and depth.

Types

The types of hypospadias are usually classified according to the position of the false meatus.

A. Balanic hypospadias.

Approximately 70 to 75 per cent of the cases are of this type. The urethral opening is below its normal location in the glans, usually at the point where the frenum is attached. Surgical intervention is rarely necessary unless the meatus is pin-point in size and requires dilation or a meatotomy.

B. Penile hypospadias.

In this instance the meatus may be observed on the under surface of the penile urethra at any point between the glans and the penoscrotal junction.

C. Perineal hypospadias.

This rarest type is noted 3 or 4 cm. from the anus and is represented as a small slit in the groove which separates the scrotum into two parts. Perineal hypospadias must be differentiated from pseudohermaphrodism which it closely resembles.

Treatment

The technical difficulties for correction of this condition, and the fact that no single operative procedure suffices for all cases is attested by the innumerable operations that have been advocated for its cor-

rection. Unsatisfactory end results can usually be attributed to two factors: first, infection; second, tension on the suture line.

Infection. Infection can usually be avoided by preserving the usual sterile technics and utilizing sterile dressings for two or three days prior to operation. I prefer moist potassium permanganate dressings. Penicillin in varying dosage is administered beginning two days before operation and continued for four or five days after operation.

Tension on the suture line. I believe that the majority of plastic procedures for the relief of hypospadias fail because of undue tension on the line of suture. Although at the end of the operation this is not evident, the first erection that occurs may cause the sutures to pull out, ruining the end results. I believe therefore that avoidance of erections is essential if satisfactory end results are to be secured. Patients are given stilbestrol (the dosage depending upon the age of the child), beginning five or six days before entering the hospital and continuing for one week after operation. The operation is not performed until the patient states that he is unable to have an erection. Pronounced improvement in the end results since stilbestrol has been advocated would indicate the importance of this preventive measure. The objectives of the plastic procedures are (1) correction of the penile curvature, and (2) construction of a urethra to the tip of the glans which will provide normal function in micturition.

The first stage of the operative procedure is the excision of the longitudinal bands of fibrous tissue which extend from the false meatus to the glans. This permits the patient to have normal erections without curvature of the penis.

Four to six months later the urethral canal is reconstructed. This may be a one or two stage procedure depending on the location of the false meatus. Suprapubic diversion of the urinary stream is not employed as the urine may be diverted through the false meatus which can be closed at a later date. I prefer the use of flaps to form the new urethra, especially since stilbestrol has come into use. The end results are more satisfactory than those obtained by the Ombrédanne technic which was employed formerly.

Conclusion

1. Stilbestrol should be administered preoperatively to patients undergoing plastic procedures for the relief of hypospadias.

2. Surgical intervention should not be instituted until the patient is unable to have an erection.

3. Penicillin minimizes the incidence of infection.

BRAIN TUMOR WITH LONG SURVIVAL OF PATIENT

Report of a Case

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This case report pertains to a retired police officer now 62 years of age. He was first seen twenty years ago in 1926 by the late Dr. T. E. Locke, who diagnosed a cystic tumor of the right parietal lobe of the brain. Some of the records were lost in the Cleveland Clinic disaster of 1929, destroying a few details of the history.

Case Report

On April 8, 1926, a man, aged 42, was referred to Cleveland Clinic. He complained of attacks of bitemporal and occipital headaches of about six months' duration, occasionally accompanied by vomiting. During the past three months a tremor and a paresis developed in the left arm and, to a lesser extent, in the left leg. These symptoms were associated with frequent attacks described by the patient as "drawing sensations". Attacks started with tingling in the finger tips of the left hand and proceeded up the arm, the left arm being drawn toward the head. The left labial commissure then drew to the left, followed by the remainder of the lower facial muscle group. At this point the patient lost consciousness and fell hard enough to injure his face. This coma apparently lasted about an hour. Vomiting occurred. Urethral and rectal sphincter control was maintained. In the last month a transient blurring of vision appeared and headaches became excruciating.

Physical examination at this time disclosed a left homonomous hemianopsia, bilateral papilledema, and retinal hemorrhages (fig. 1). The lower facial muscles, arm, and leg exhibited weakness on the left side. A marked tremor of the left arm was evident.

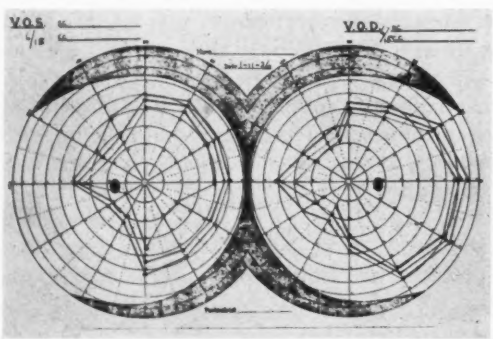

FIG. 1. Visual fields showing left homonomous hemianopsia.

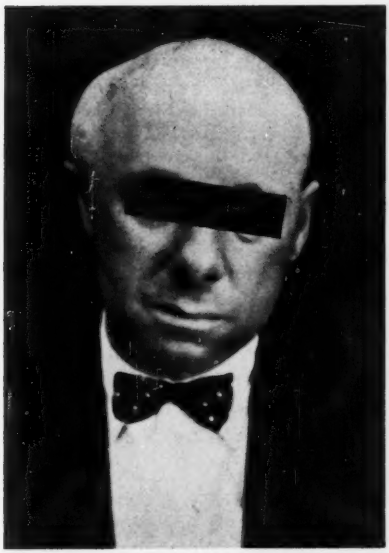

FIG. 2. Photograph of patient showing herniation at site of craniotomy

Tactile sense was diminished over the left arm and leg. The deep reflexes of the left arm were exaggerated. The left cremasteric and plantar reflexes were diminished.

A diagnosis of right parietal lobe tumor was made. A cranioplasty and drainage of one or two cysts was performed by Dr. Locke on April 14, 1926, relieving the increased intracranial pressure. No further procedures were considered necessary, and the wound was closed without exposing the tumor.

A few months following operation there was considerable herniation of brain tissue through the cranial defect (fig. 2). At this time a course of roentgen therapy was given. The details of technic are not available. The patient was later given another course of roentgen therapy, after which the herniation disappeared.

On two occasions, November 29, 1926, and August 1, 1927, it became necessary to aspirate a cystic area in the tumor, and about 60 cc. of a viscid yellow fluid was removed each time. No biopsy report is available, but the clinical impression was cystic astrocytoma.

Two years later the patient suffered a return of the previous attacks on three occasions within the two months. At examination, serologic examinations were negative, blood cell studies normal, and blood sugar test 78 mg. per cent. There was no evidence of increased intracranial pressure nor herniation. A sedative of the barbital series was prescribed to control the symptoms.

The patient resumed his work on the police force and in 1940, fourteen years after his initial visit, was doing light work at the age of 56. In June, 1940, however, he experienced two more attacks within three days. Examination revealed the decompression flat and soft. Gait of the patient appeared normal, and no evidence of disability in the

left arm or leg was noted except for a slight exaggeration of the tendon reflexes. Sedation was again advised.

The patient was last seen on January 29, 1945, over eighteen years after his first visit, at which time he complained of severe sharp pains over the right forehead, upper jaw, and cheek. Pains appeared suddenly and lasted from a few seconds to a minute. The left homonomous hemianopsia remained. In addition the patient noticed blue and red flashes to his left. He had remained free of convulsions for the four and a half years since his last previous visit. The decompression remained soft and flat. The optic disks were normal. The new symptoms were explained on a sensory jacksonian basis. No treatment beyond mild sedation was recommended.

Discussion

This report presents the history of a patient with a cystic tumor, probably an astrocytoma, in the right parietal lobe of the brain. Surgical treatment consisted of decompression followed by aspiration of the cyst on two occasions. Radiation treatment was given at intervals and appeared to account to some extent for the regression of symptoms and for the long survival.

In our experience the usual course of even the slow-growing fibrillary astrocytoma is about ten years. As some of the records have been lost, the microscopic picture and exact diagnosis cannot be given in this case.

Erratum

On page 31 of the January, 1947, issue of the *Quarterly*, in the second line of the legend the word *jejunum* should be substituted for *duodenum*, making the legend read: *Radical resection of head of pancreas and duodenum, showing gastroenterostomy and implantation of pancreatic and biliary ducts into jejunum.*

On page 45, in line 17 the figure *1000* should be substituted for *10,000*, making the line read, *a total dose of 1200 r. and the spinal areas each 1000 r . . . .*